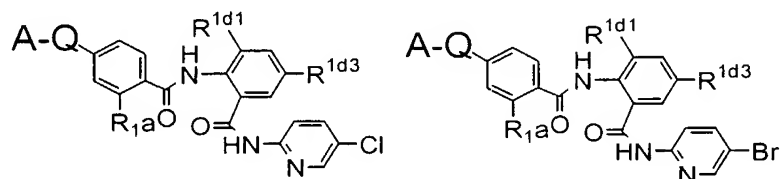


100

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

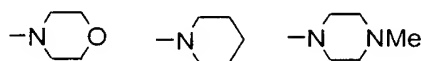
The invention provides compound of formula Ib, as described above, having
5 the following structure:



wherein:

R^{1a} is H or F;

R^{1d1} is selected from H, -OMe, -NMe₂,

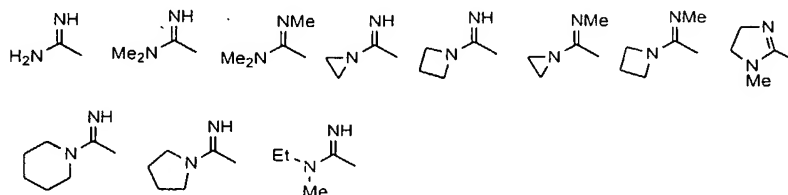


-N(Me)COOH, -N(Me)COOEt ;

10

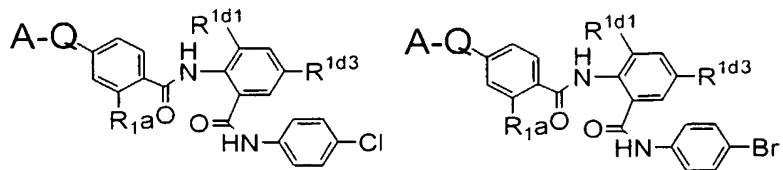
R^{1d3} is Cl or Br;

A-Q is a member selected from the group consisting of:



15 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having
the following structure:



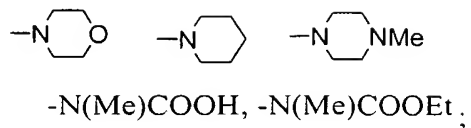
20

101

wherein:

R^{1a} is H or F;

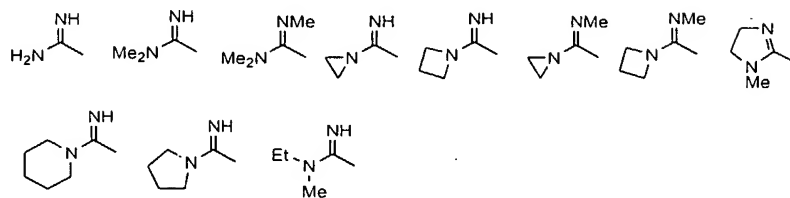
R^{1d1} is selected from H, -OMe, -NMe₂,



5

R^{1d3} is Cl or Br;

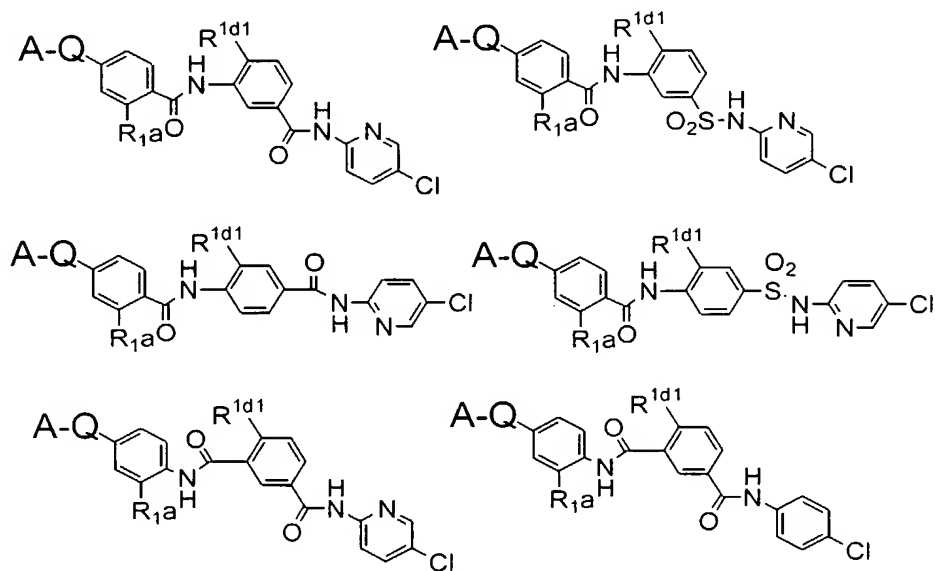
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

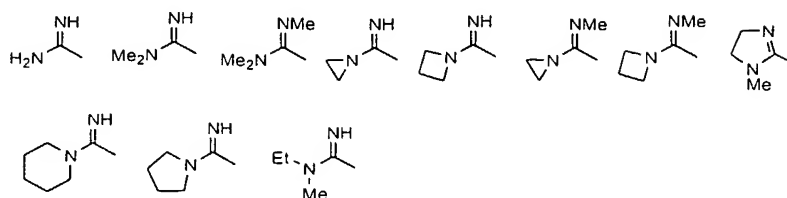
10

The invention provides compound of formula Ib, as described above, having the following structure:



15

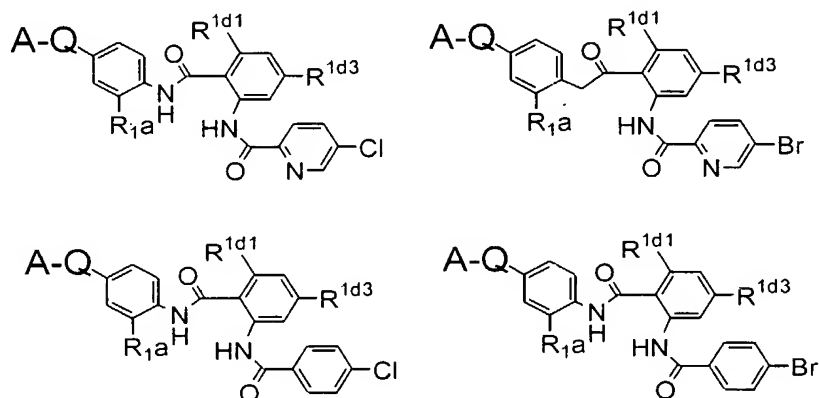
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5

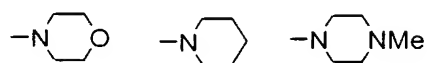
The invention provides a compound of formula Ib, as described above, having the following structure:



wherein:

10 R^{1a} is H or F;

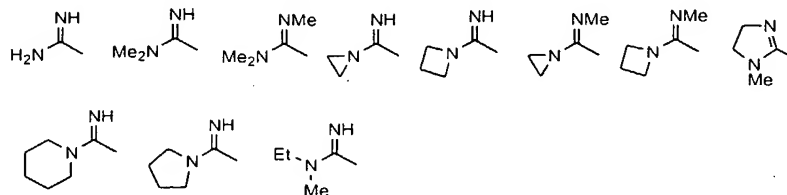
R^{1d1} is selected from H, -OMe, -NMe₂,



-N(Me)COOH, -N(Me)COOEt ; and

R^{1d3} is -Cl or -Br,

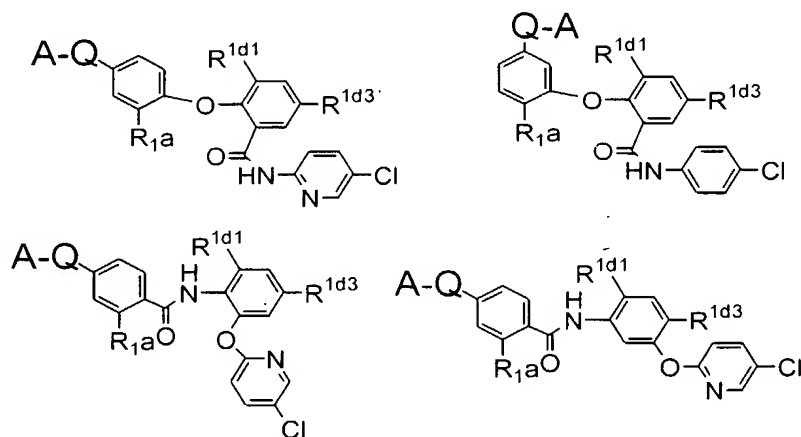
A-Q is a member selected from the group consisting of:



15

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

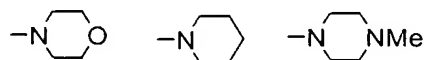
The invention provides compound of formula Ib, as described above, having
5 the following structure:



wherein:

R^{1a} is H or F;

R^{1d1} is selected from H, -OMe, -NMe₂,

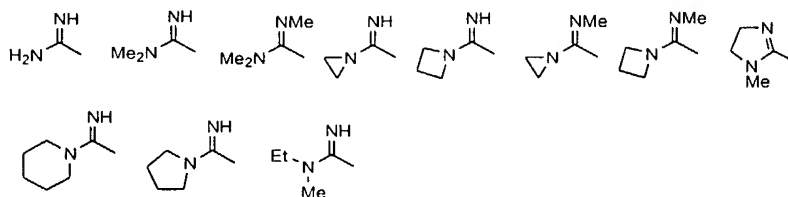


10

-N(Me)COOH, -N(Me)COOEt ; and

R^{1d3} is -Cl or -Br,

A-Q is a member selected from the group consisting of:

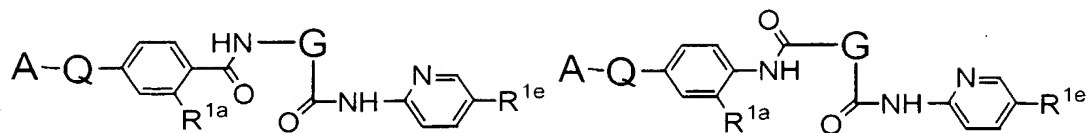


15

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

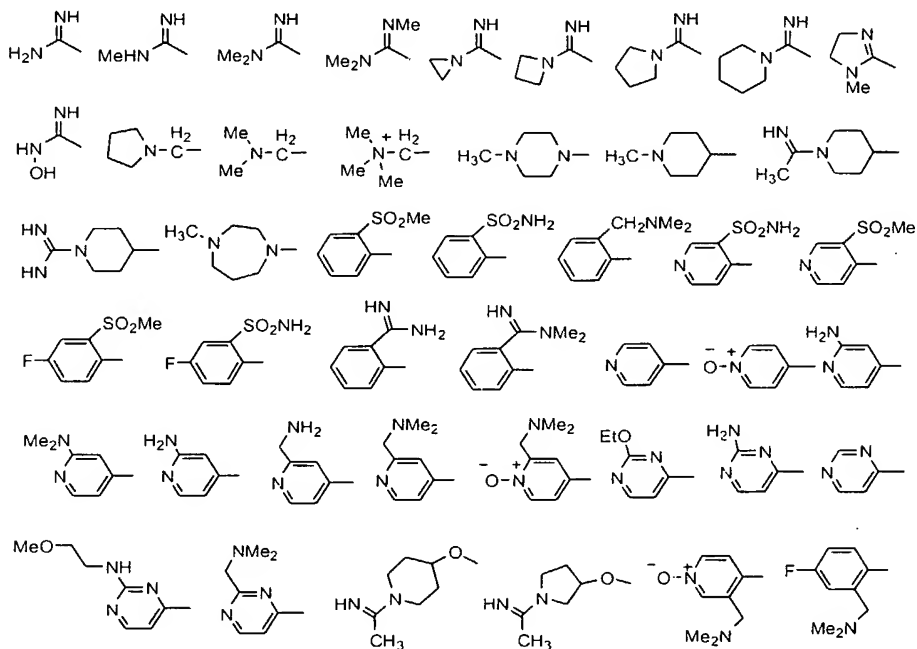
The invention provides compound of formula Ib, as described above, having
the following structure:

105



wherein:

A-Q is a member selected from the group consisting of:



5

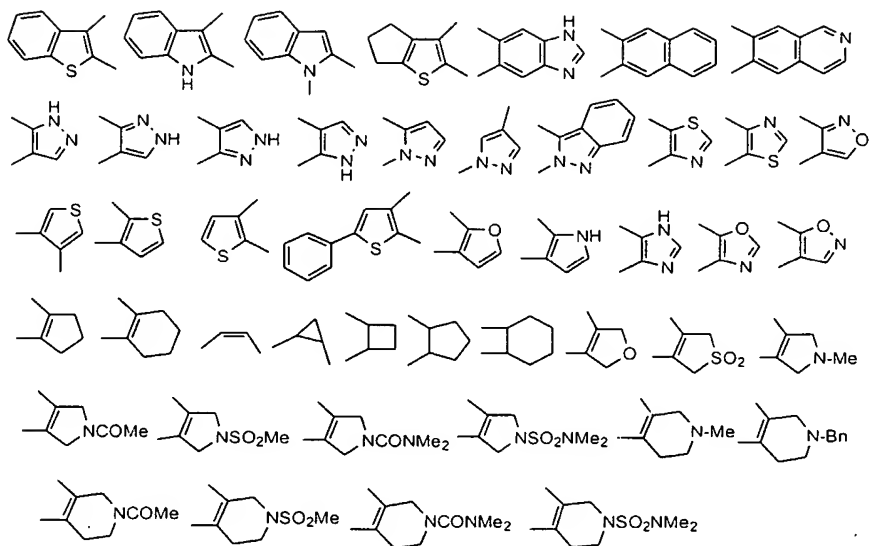
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

R^{1c} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂; and

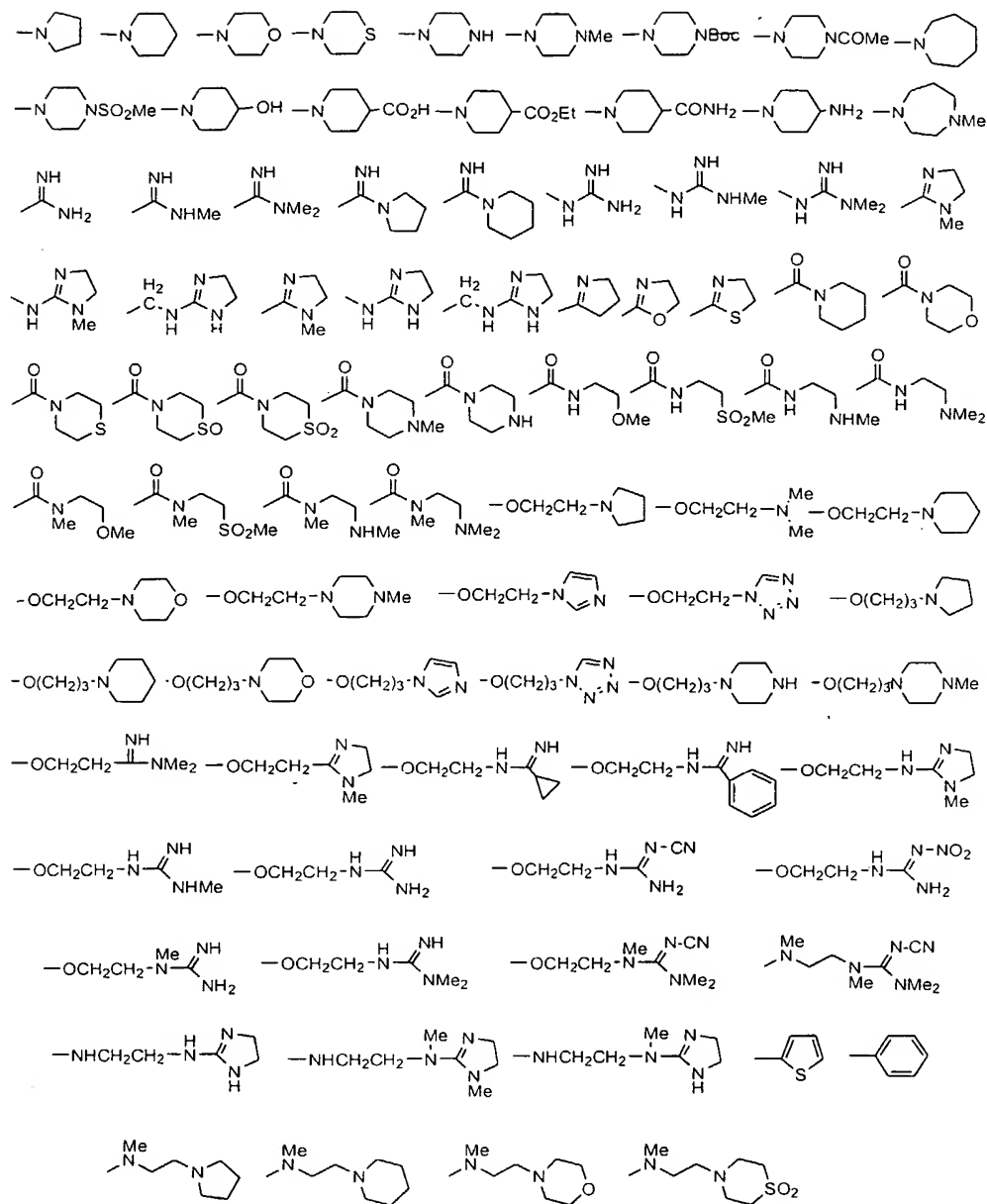
10 G is a member selected from the group consisting of:



wherein each G group is substituted by 0-4 R^{ld} groups and each such R^{ld} group is independently selected from the group consisting of:

- 5 H, -Me, -F, -Cl, -Br, aryl, heteroaryl, -NH₂, -NMe₂, -NHMe, -NHSO₂Me, -NHCOMe, -CH₃, -CF₃, -OH, -OCH₃, -SCH₃, -OCF₃, -OCH₂F, -OCHF₂, -OCH₂CF₃, -OCF₂CF₃, -NO₂, -CN, -CO₂H, -CO₂Me, -CO₂Et, -CONH₂, -CONHMe, -CONMe₂, -SO₂NH₂, -SO₂CH₃, -SO₂NMe₂, -CH₂OH, -CH₂NH₂, -CH₂NHMe, -CH₂NMe₂, -OCH₂CO₂H, -OCH₂CO₂Me, -OCH₂CO₂Et, -OCH₂CONH₂, -OCH₂CONMe₂, -OCH₂CONHMe, -OCH₂CH₂OMe, -OCH₂CH₂OEt, -OCH₂CH₂NH₂, -OCH₂CH₂NHMe, -OCH₂CH₂NMe₂, -NHCH₂CH₂OMe, -SCH₂CH₂OMe, -SO₂CH₂CH₂OMe, -OCH₂CH₂SO₂Me, -NHCH₂CH₂NHMe, -NHCH₂CH₂NMe₂, -N(CH₂CH₂OH)₂, -N(CH₂CH₂OMe)₂, -NHCH₂CO₂H, -NHCH₂CO₂Et, -NHCH₂CO₂Et, -NHCH₂CONH₂, -NHCH₂CONMe₂, -NHCH₂CONHMe, -N(CH₃)CH₂CO₂H, -N(CH₃)CH₂CO₂Et, -(NMe)CH₂COOH, -N(Me)CH₂CONH₂, -N(Me)CH₂CH₂NMe₂, -N(Me)CH₂CH₂OMe, -NHCH₂CH₂OMe,
- 10
- 15

107

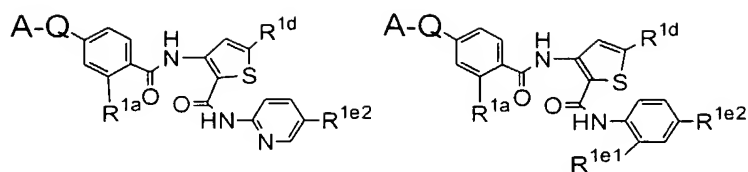


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5

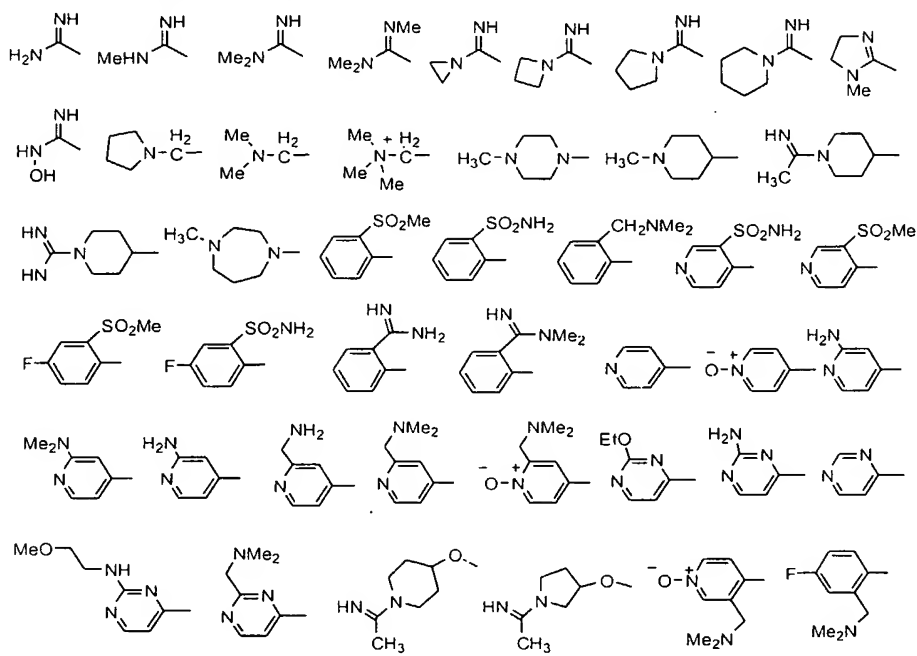
The invention provides compound of formula Ib, as described above, having the following structure:

108



wherein:

A-Q is a member selected from the group of:



5

R^{1a} is a member selected from the group of:

H, -F, -Cl, -Br;

R^{1d} is a member selected from the group of:

H, -F, -Cl, -Br, -OMe;

10 R^{1e1} is a member selected from the group of:

H, -F, -Cl, -Br, -NH₂, -CH₂NH₂, -OMe, -OH, -CN, -SO₂Me, -SO₂NH₂; and

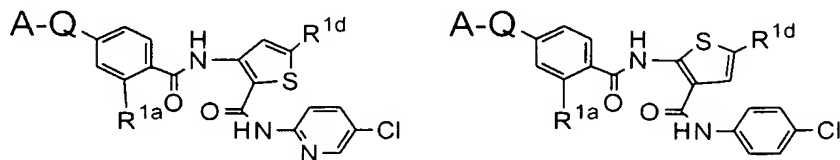
R^{1e2} is a member selected from the group of:

H, -F, -Cl, -Br, -NH₂,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug

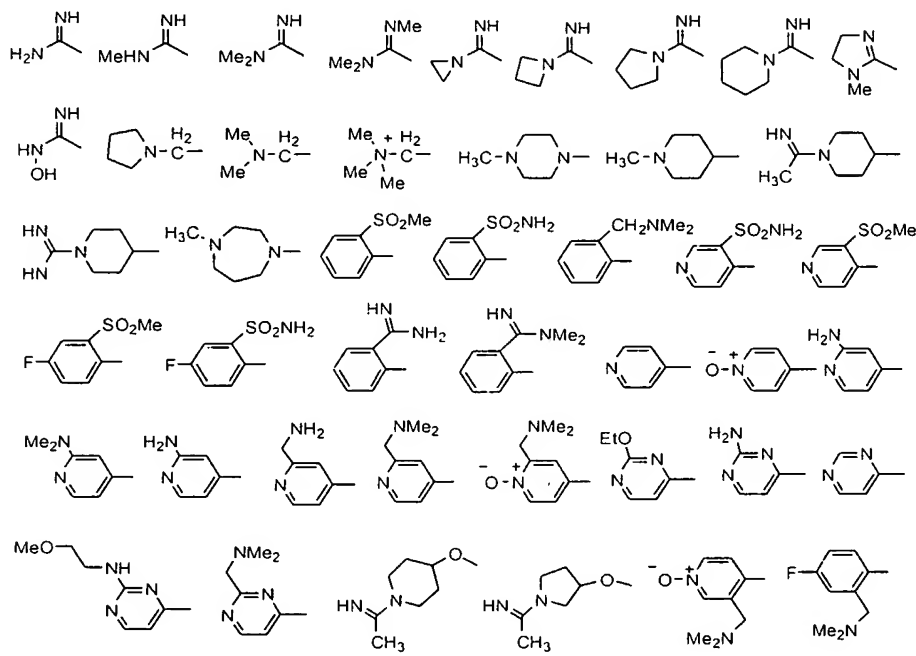
15 derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

- 5 A-Q is a member selected from the group of :



R^{1a} is a member selected from the group of:

H, -F, -Cl and Br; and

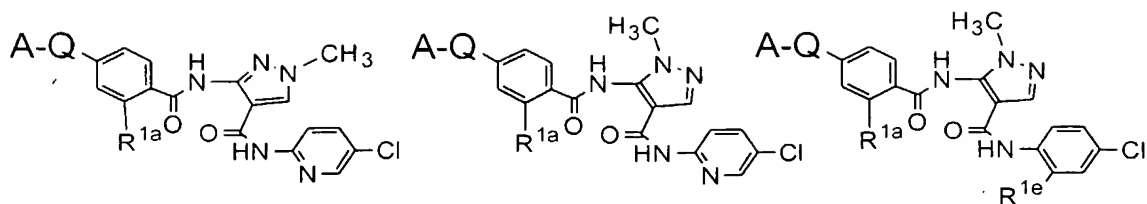
R^{1d} is a member selected from the group of:

- 10 H, -F, -Cl, -Br, -OMe,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

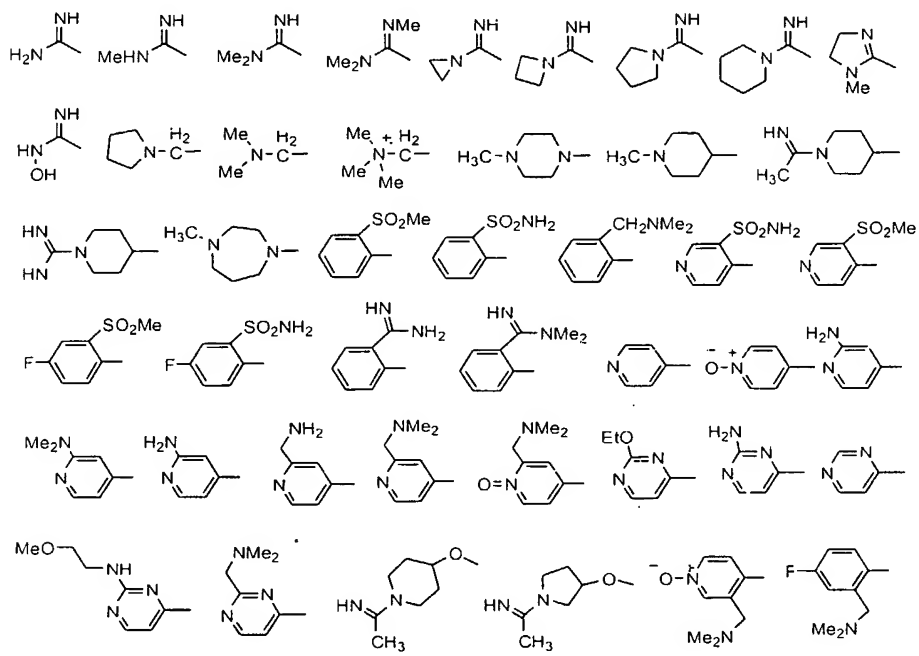
- 15 The invention provides compound of formula Ib, as described above, having the following structure:

110



wherein:

A-Q is a member selected from the group of :



5

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br; and

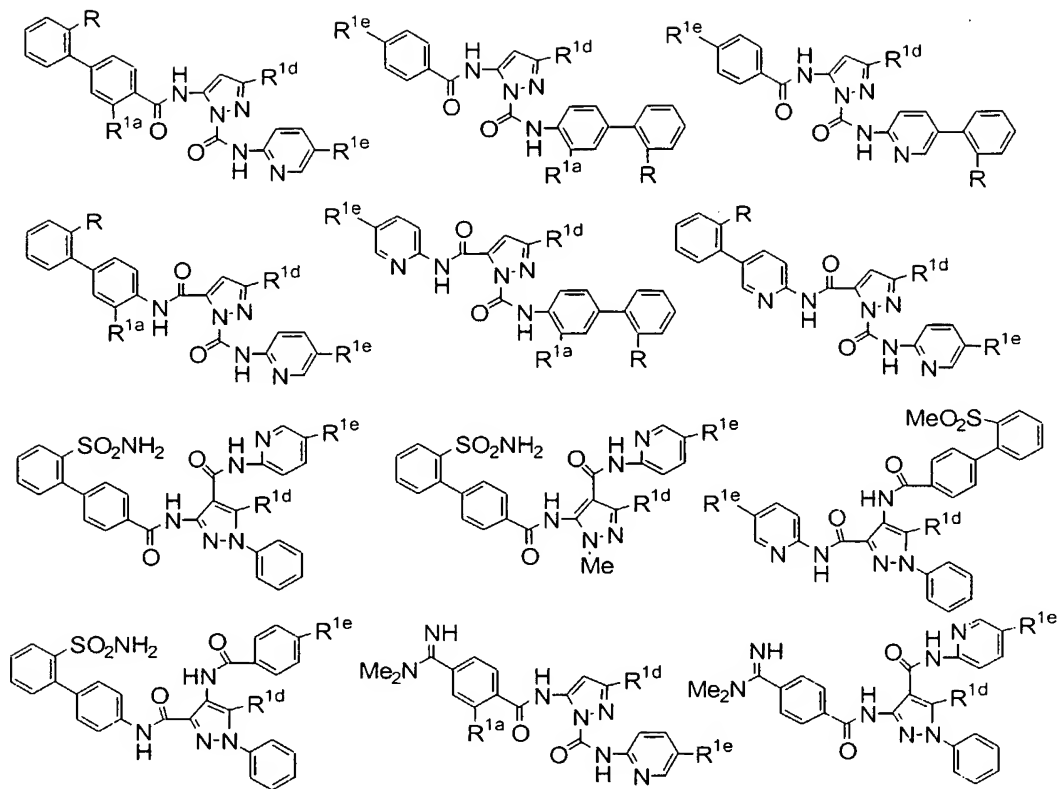
R^{1c} is a member selected from the group of:

H, -F, -Cl, -Br, -NH₂, -CH₂NH₂, -OMe, -OH, -CN, -SO₂Me, -SO₂NH₂,

10 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

15



wherein:

R is a member selected from the group of :

-SO₂NH₂, -SO₂Me, -CH₂NMe₂;

5 R^{1a} is a member selected from the group of:

H, -F, -Cl, -Br;

R^{1d} is a member selected from the group of:

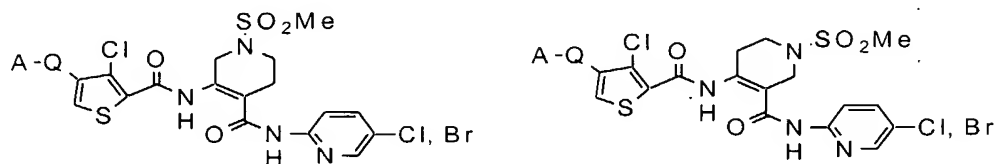
H, -F, -Cl, -Br, -CN, CF₃, -CH₃, -SO₂NH₂, -SO₂Me; and

R^{1e} is a member selected from the group of:

10 -Cl, -Br,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

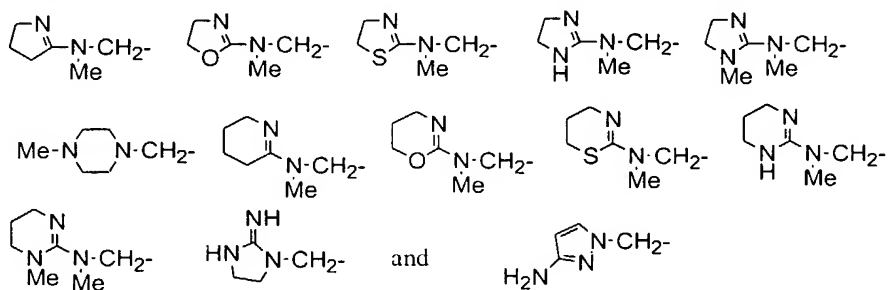
The invention provides compound of formula Ib, as described above, having the following structure:



5

wherein:

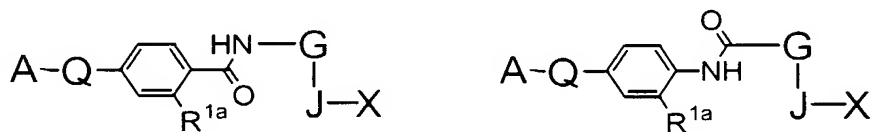
A-Q taken together are a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

10

The invention provides compound of formula Ib, as described above, having the following structure:

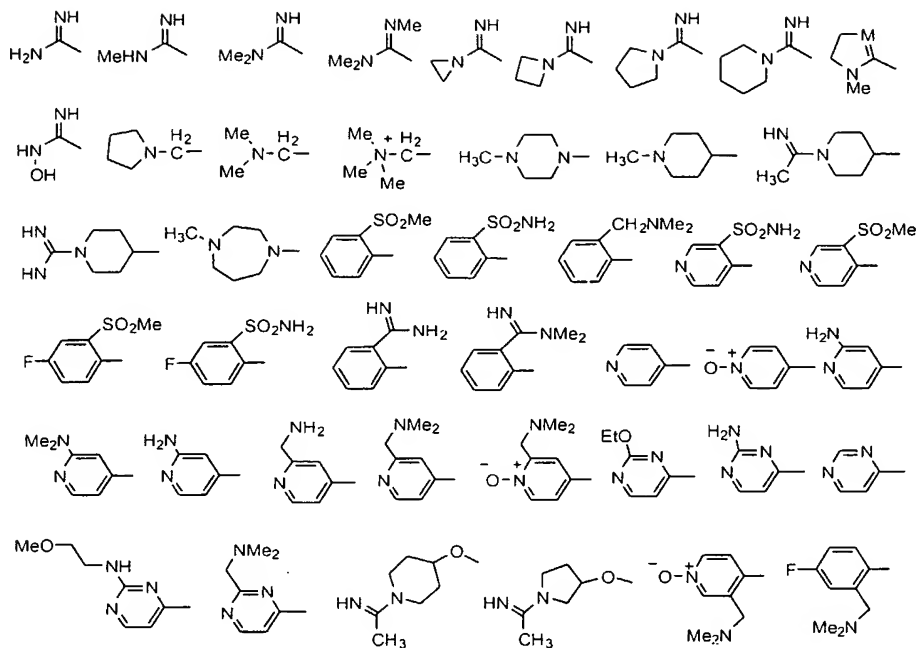


15

wherein:

A-Q is a member selected from the group consisting of:

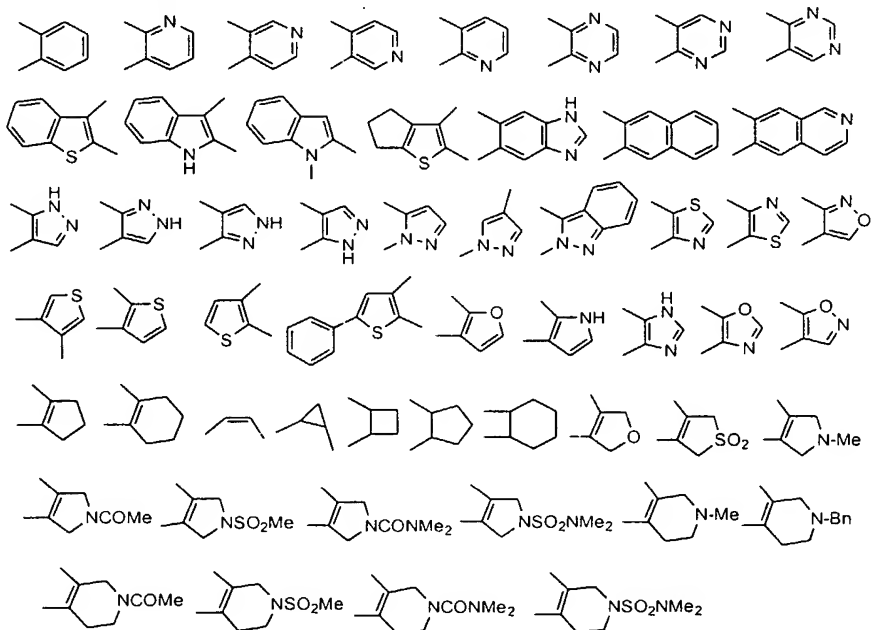
113



R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

G is a member selected from the group consisting of:



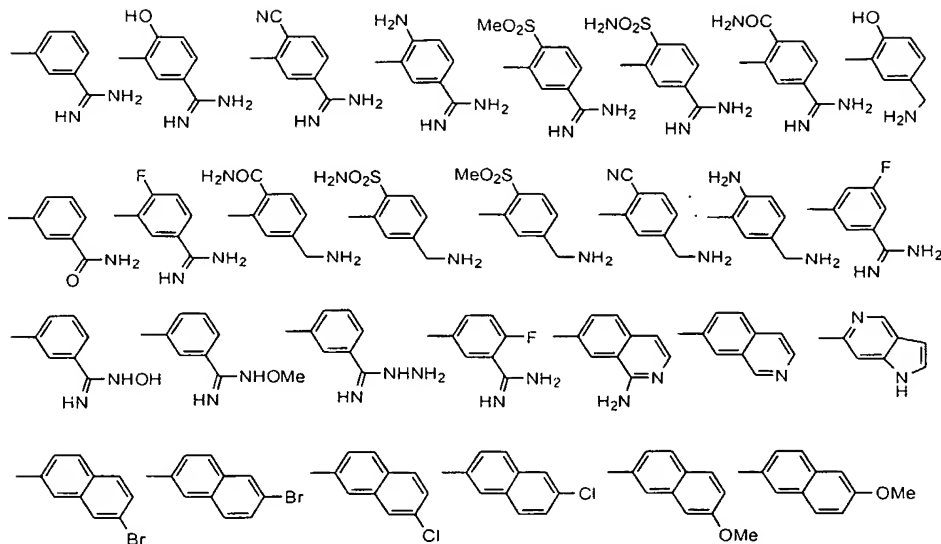
5

wherein each G group is substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

- H, -Me, -F, -Cl, -Br, aryl, heteroaryl, -NH₂, -NMe₂, -NHMe, -NHSO₂Me, -NHCOMe, -CH₃, -CF₃, -OH, -OCH₃, -SCH₃, -OCF₃, -OCH₂F, -OCHF₂, -OCH₂CF₃, -OCF₂CF₃, -NO₂, -CN, -CO₂H, -CO₂Me, -CO₂Et, -CONH₂, -CONHMe, -CONMe₂, -SO₂NH₂, -SO₂CH₃, -SO₂NMe₂, -CH₂OH, -CH₂NH₂,
5 -CH₂NHMe, -CH₂NMe₂, -OCH₂CO₂H, -OCH₂CO₂Me, -OCH₂CO₂Et, -OCH₂CONH₂, -OCH₂CONMe₂, -OCH₂CONHMe, -OCH₂CH₂OMe, -OCH₂CH₂OEt, -OCH₂CH₂NH₂, -OCH₂CH₂NHMe, -OCH₂CH₂NMe₂, -NHCH₂CH₂OMe, -SCH₂CH₂OMe, -SO₂CH₂CH₂OMe, -OCH₂CH₂SO₂Me, -NHCH₂CH₂NHMe, -NHCH₂CH₂NMe₂, -N(CH₂CH₂OH)₂, -
10 N(CH₂CH₂OMe)₂, -NHCH₂CO₂H, -NHCH₂CO₂Et, -NHCH₂CO₂Et, -NHCH₂CONH₂, -NHCH₂CONMe₂, -NHCH₂CONHMe, -N(CH₃)CH₂CO₂H, -N(CH₃)CH₂CO₂Et, -(NMe)CH₂COOH, -N(Me)CH₂CONH₂, -N(Me)CH₂CH₂NMe₂, -N(Me)CH₂CH₂OMe, -NHCH₂CH₂OMe,

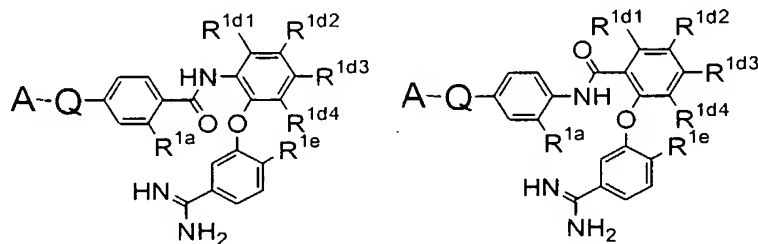
-CONH-, -NHCO-, -O-, -NH-, -NMe-, -CONMe-, -NMeCO-; and

X is a member selected from the group consisting of:



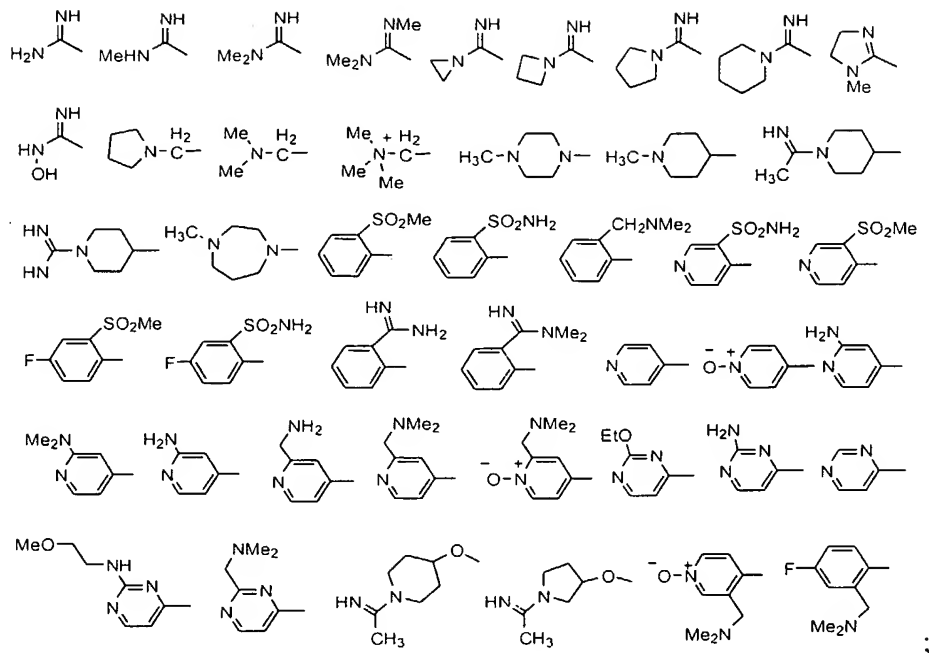
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

- 5 The invention provides compound of formula Ib, as described above, having the following structure :



wherein:

A-Q is a member selected from the group of:







R^{1a} is a member selected from the group of:

H, -F, -Cl, -Br;

$R^{1d1}, R^{1d2}, R^{1d3}$ and R^{1d4} is independently a member selected from the group of:

5 H, -F, -Cl, -Br, -NO₂, -NH₂, -NHMe, -NMe₂, -NHAc, -NHSO₂Me, -SO₂Me, -CO₂H, -CO₂Me, -OH, -OMe, -N(Me)CO₂H, -N(Me)CO₂Et and

—N—  N—CH_3 —N—  —N—  NH— —N—  O— ; and

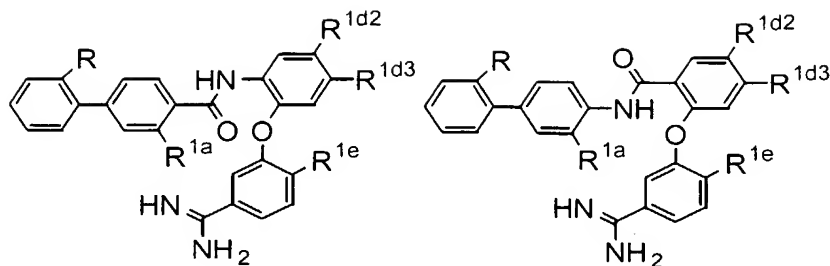
R^{le} is a member selected from the group of:

 H, -OH,

10 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

118



R is a member selected from the group of:

-SO₂Me, -SO₂NH₂, -CH₂NH₂, -CH₂N(CH₃)₂;

R^{1a} is a member selected from the group of:

5 H, -F;

R^{1d2} and R^{1d3} is independently a member selected from the group of:

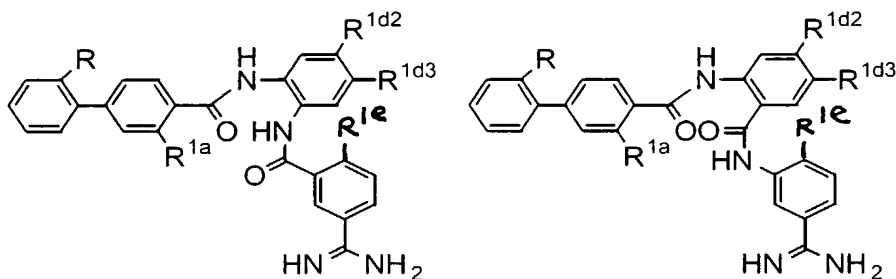
H, -F, -Cl, -Br, -NO₂, -NH₂, -NHMe, -NMe₂, -NHAc, -NHSO₂Me, -SO₂Me,
-CO₂H, -CO₂Me, -OH, -OMe; and

R^{1e} is a member selected from the group of:

10 H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having
15 the following structure:



wherein:

R is a member selected from the group of:

-SO₂Me, -SO₂NH₂, -CH₂NH₂, -CH₂N(CH₃)₂;

20 R^{1a} is a member selected from the group of:

H, -F;

R^{1d2} and R^{1d3} is independently a member selected from the group of:

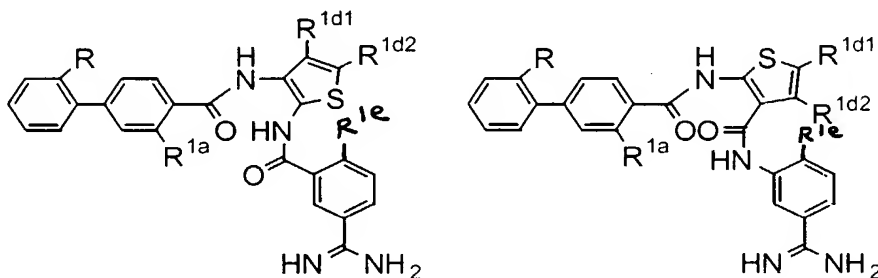
H, -F, -Cl, -Br, -NO₂, -NH₂, -NHMe, -NMe₂, -NHAc, -NHSO₂Me, -SO₂Me, -CO₂H, -CO₂Me, -OH, -OMe; and

R^{1e} is a member selected from the group of:

5 H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having
10 the following structure:



R is a member selected from the group of:

-SO₂Me, -SO₂NH₂, -CH₂NH₂, -CH₂N(CH₃)₂;

15 R^{1a} is a member selected from the group of:

H, -F;

R^{1d1} and R^{1d2} is independently a member selected from the group of:

H, -F, -Cl, -Br, -OMe; and

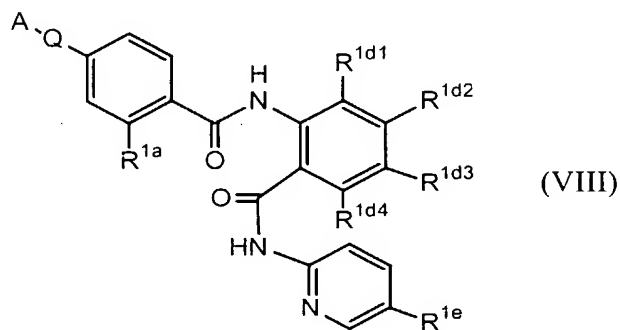
R^{1e} is a member selected from the group of:

20 H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The following preferred embodiments of the present invention illustrate compounds wherein the central aromatic ring structure is divalent phenylene, however divalent 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms may be substituted for the bivalent phenylene structure. Further the terminal aromatic ring substituted which is substituted by a R^{1e} group as illustrated below in the preferred embodiments is either a phenyl or a 2-pyridyl group, however other 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms can be substituted for either the phenyl or 2-pyridyl. Moreover, 2 to 3 additional R^{1e} groups other than hydrogen may each be independently substituted for a hydrogen atom attached to a ring carbon on the terminal rings illustrated or substituted for the illustrated terminal ring structure.

A preferred embodiment of the invention provides a compound of formula VIII:



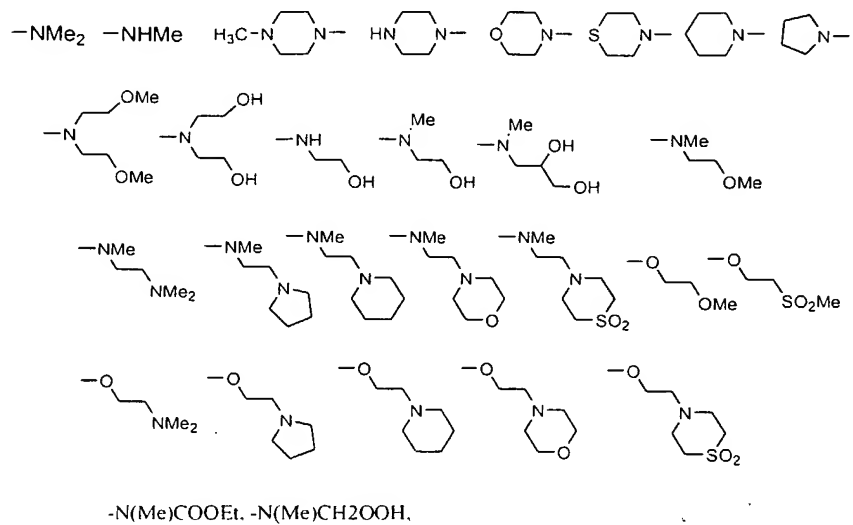
wherein:

R^{1a} is a member selected from the group of H, -F, -Cl and Br;

R^{1d2} and R^{1d4} are each H or F;

121

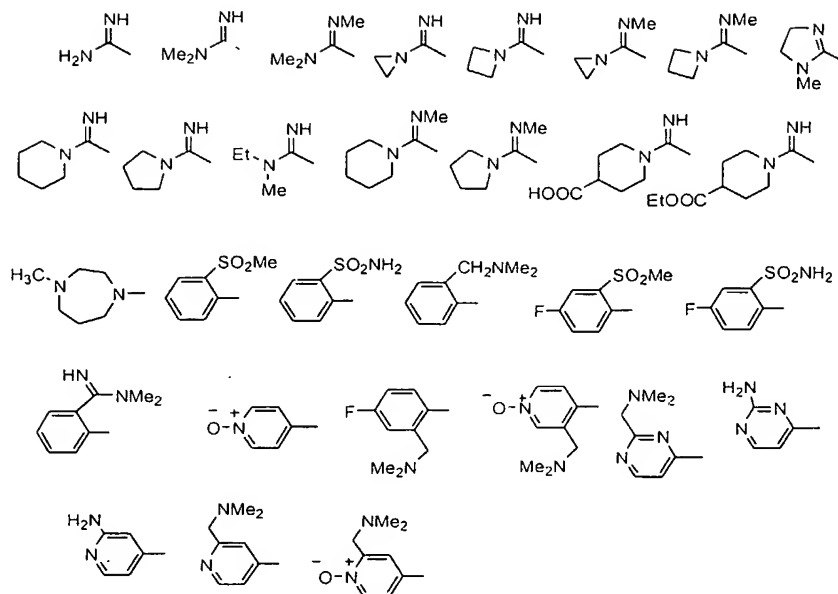
R^{1d1} and R^{1d3} are each independently a member selected from the group of H, -Cl, -F, -Br, -OH, -OMe, -OCF₃, OCHF₂, OCH₂F, -NH₂, -NMe₂, -OCH₂COOEt, -OCH₂COOH, -N(Me)CH₂COOH, -N(Me)COOEt, and,



5

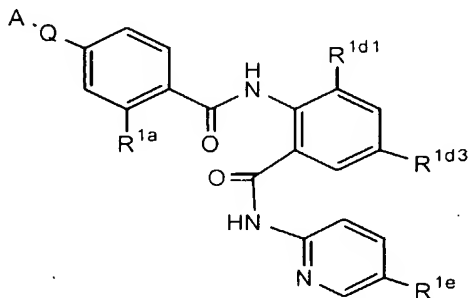
R^{1c} is a member selected from the group of -F, -Cl, -Br, -OH, -Me and -OMe;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

- 5 Another preferred embodiment provides a compound of formula VIII having the following structure:

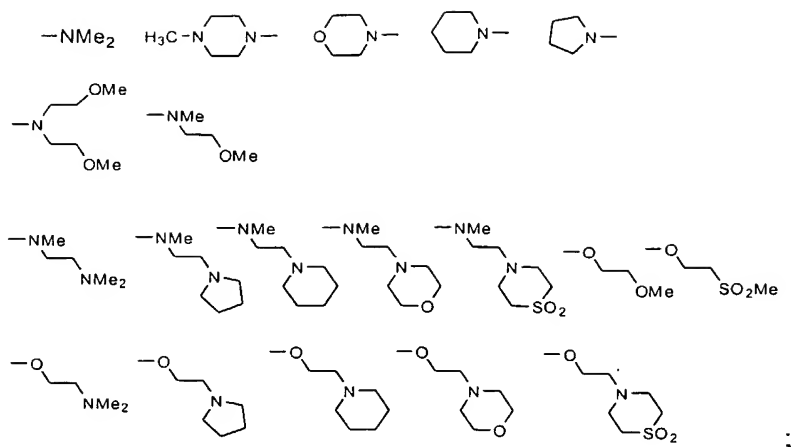


wherein:

R^{1a} is a member selected from the group of H, or -F;

- 10 R^{1d1} is each independently a member selected from the group of H, -Cl, -OMe, -NMe₂, -OCH₂COOEt, -OCH₂COOH, -N(Me)CH₂COOH, -N(Me)COOEt,

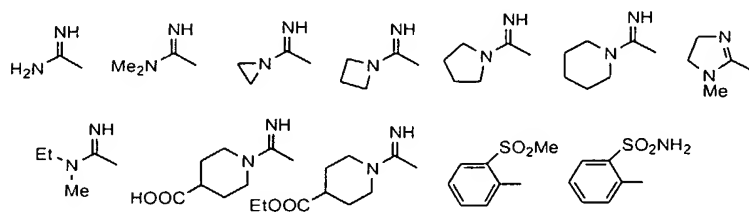
123



R^{1d3} are independently a member selected from the group of H, -Cl, -Br, -F, and -OMe;

5 R^{1e} is a member selected from the group of -Cl, and -Br;

A-Q is a member selected from the group consisting of:

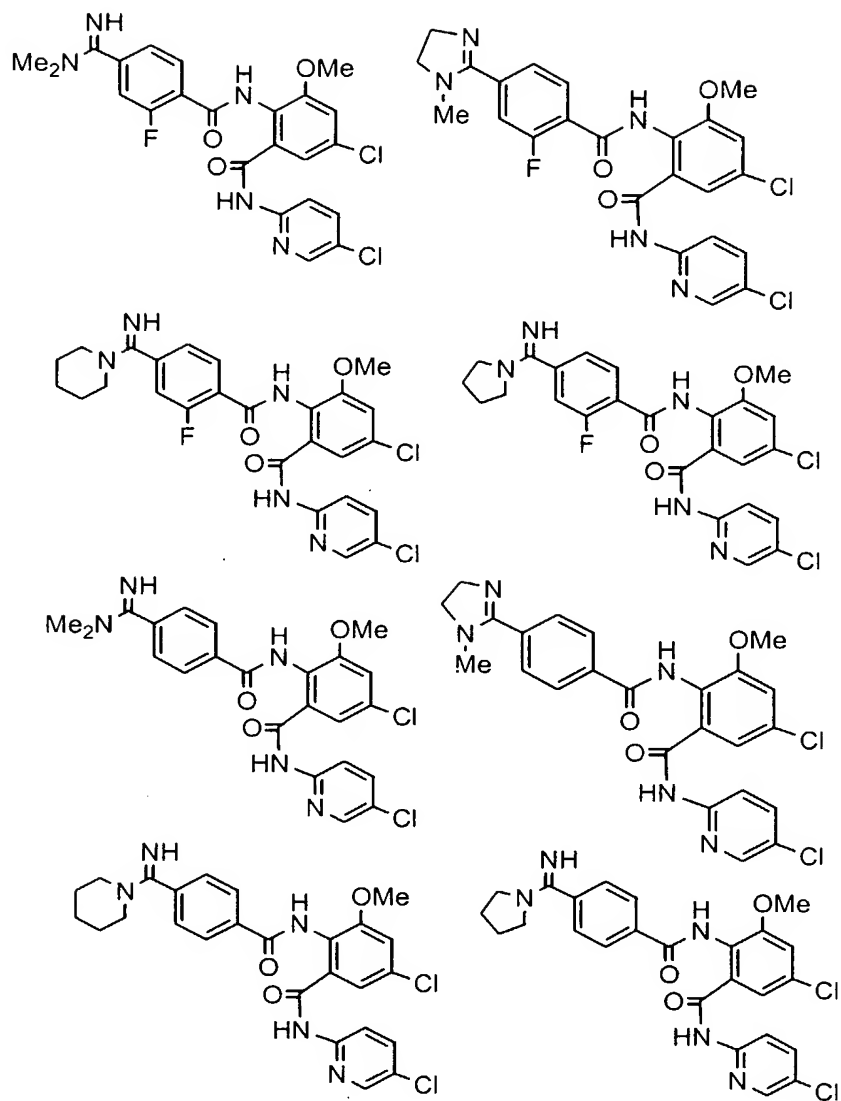


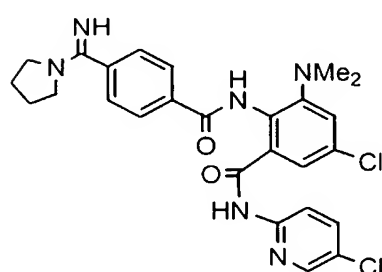
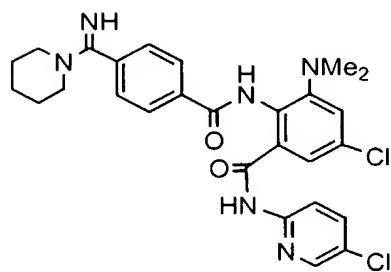
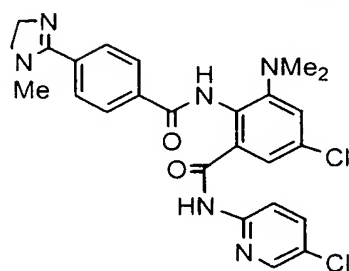
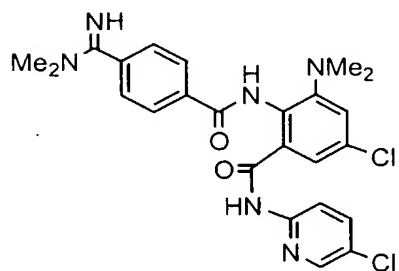
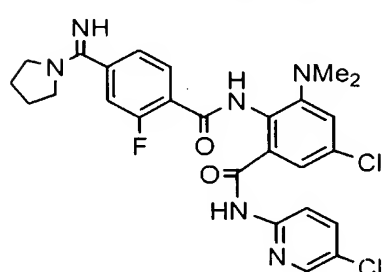
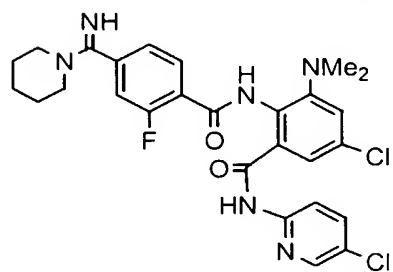
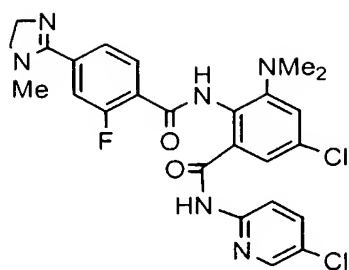
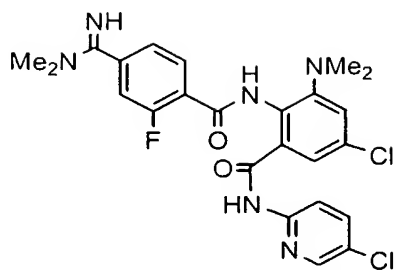
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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

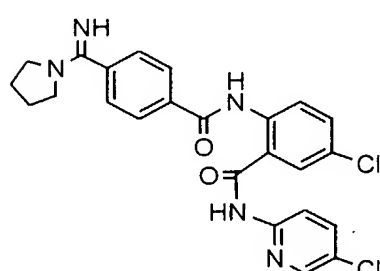
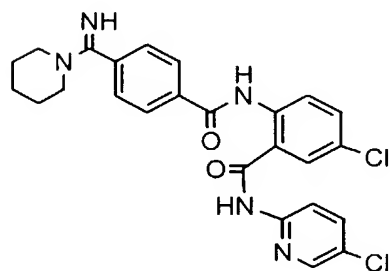
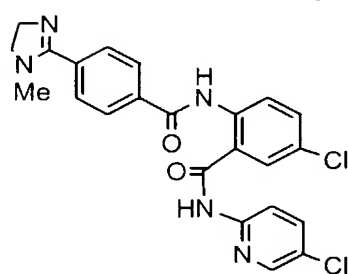
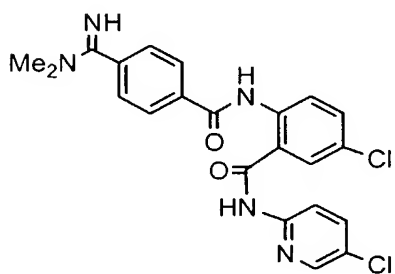
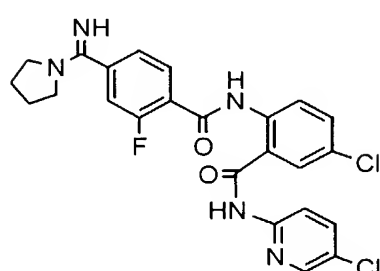
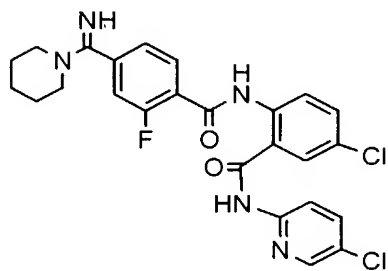
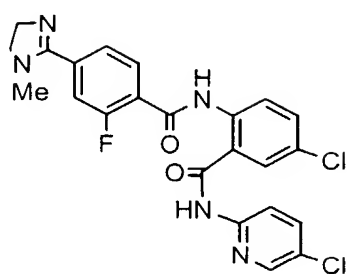
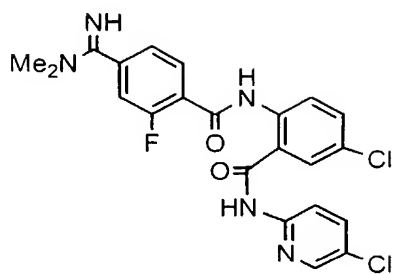
Another preferred embodiment according to the present invention provides an
15 individual compound, which is a member selected from the following structures:

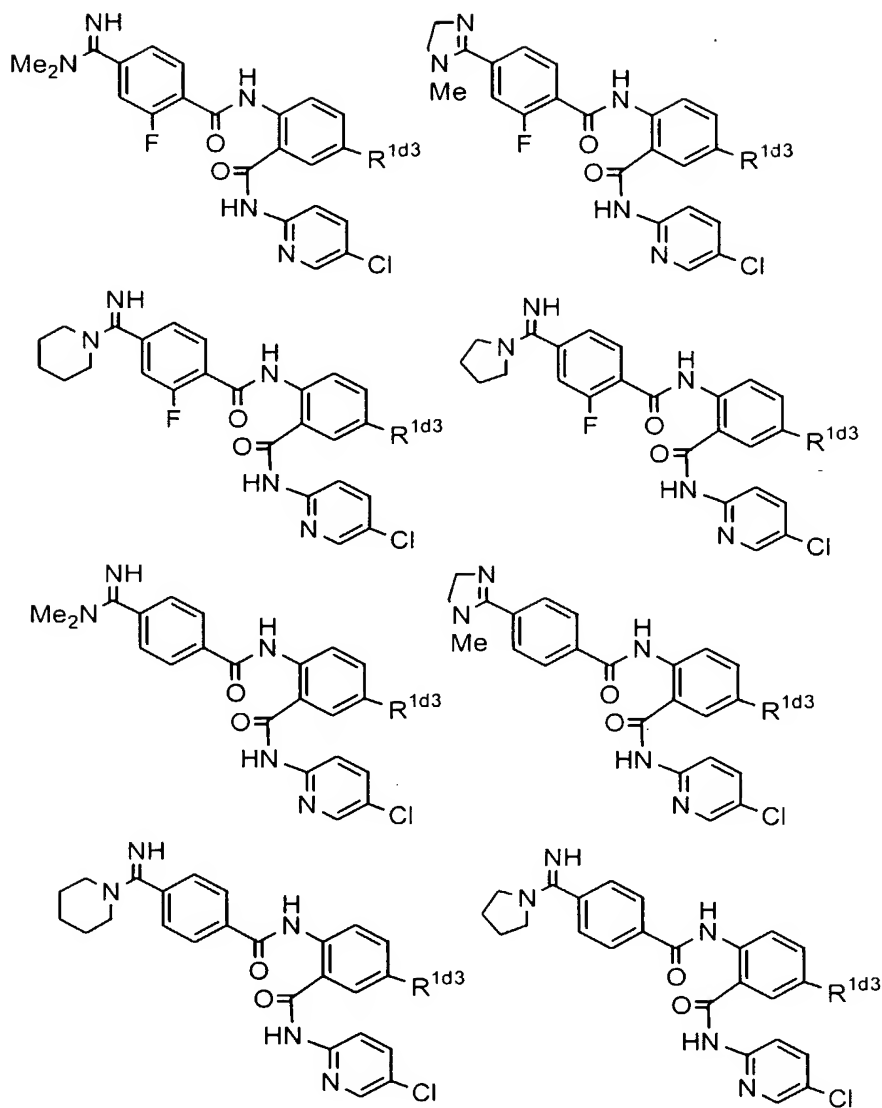
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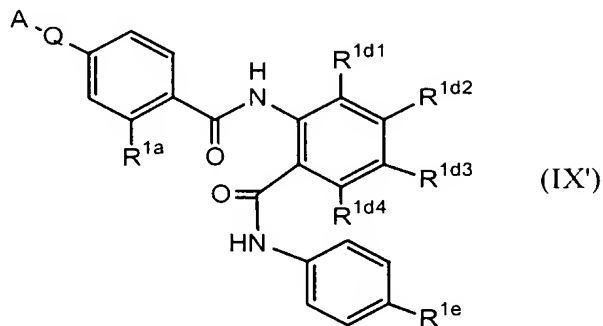
wherein

R^{ld3} is a member selected from the group consisting of:

- 5 H, -F, -Cl, -Br, -OMe, -OCF₃, -OCF₂H, and -OCF₂H;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A still further embodiment of the present invention provides a compound according to the formula IX, as follow:



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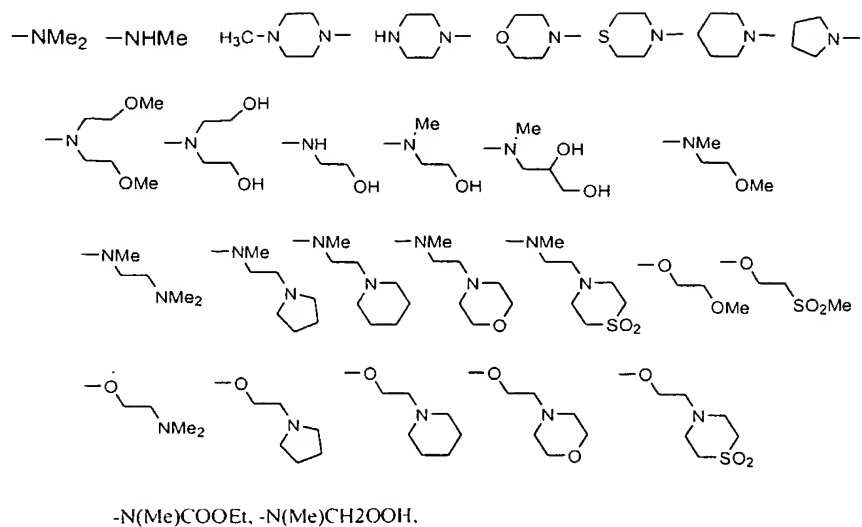
wherein:

R^{1a} is a member selected from the group of H, -F, -Cl and Br;

R^{1d2} and R^{1d4} are each H or F;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H,
 10 -Cl, -F, -Br, -OH, -OMe, -OCF₃, OCHF₂, OCH₂F, -NH₂, -NMe₂, -OCH₂COOEt, -
 OCH₂COOH, - N(Me)CH₂COOH, -N(Me)COOEt,

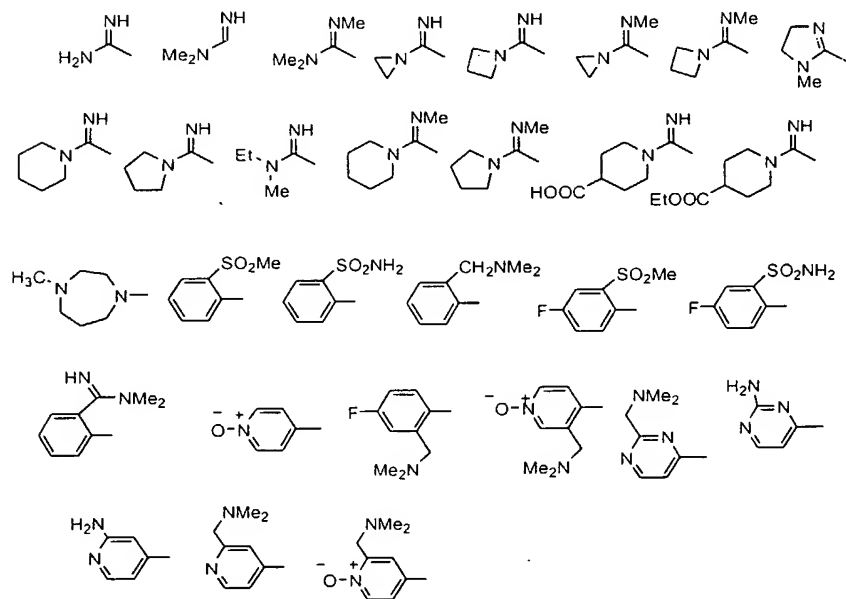
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R^{1e} is a member selected from the group of -F, -Cl, -Br, -OH, -Me and -OMe;

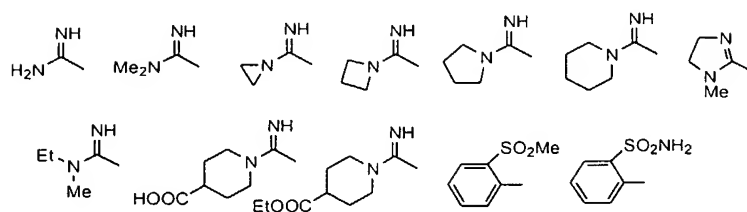
5

A-Q is a member selected from the group consisting of:



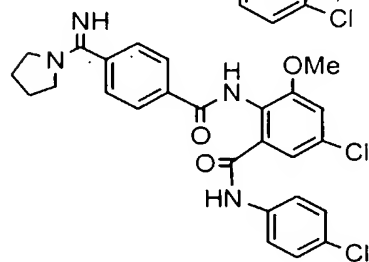
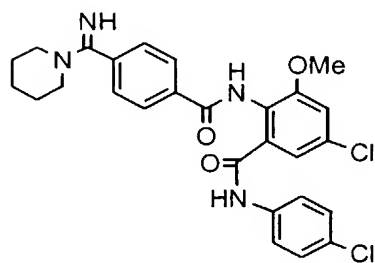
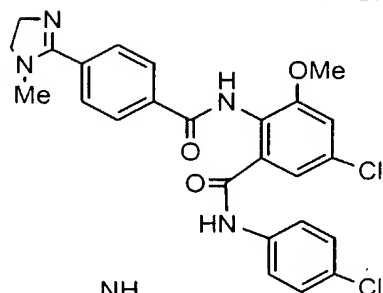
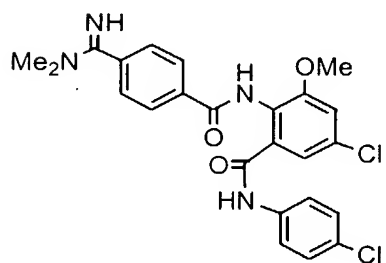
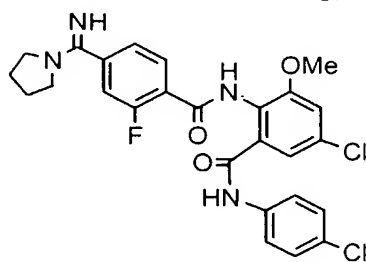
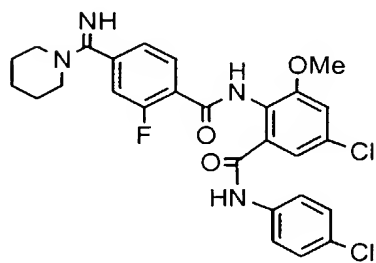
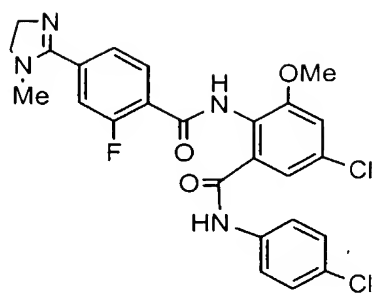
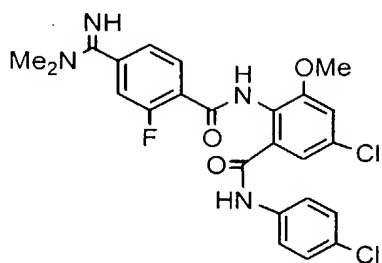
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5 A-Q is a member selected from the group consisting of:

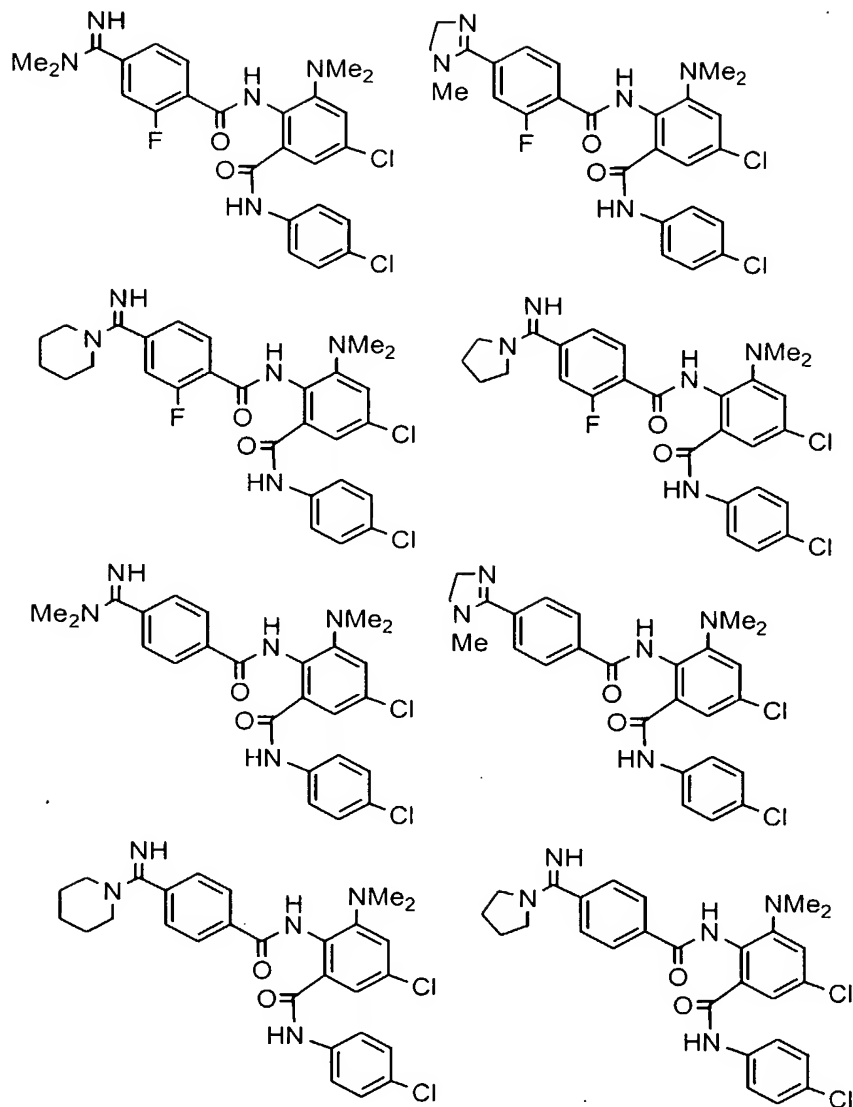


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug
10 derivatives thereof.

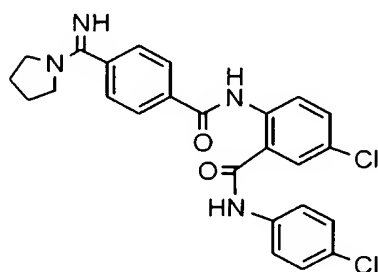
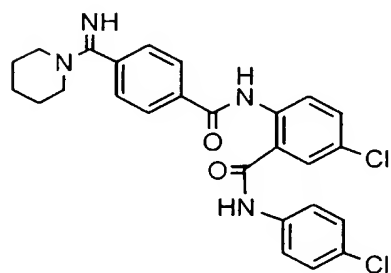
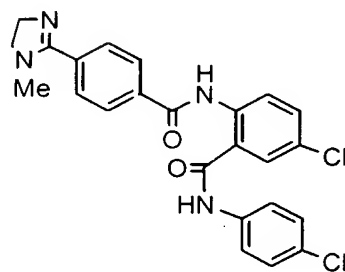
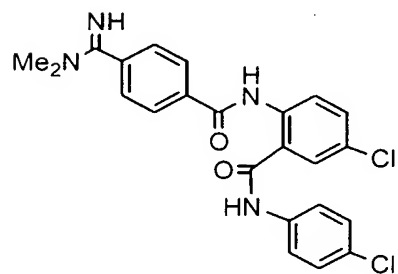
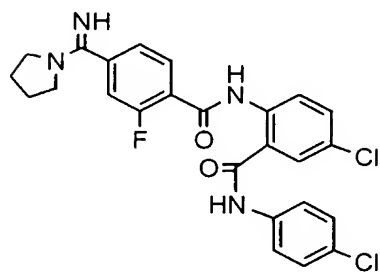
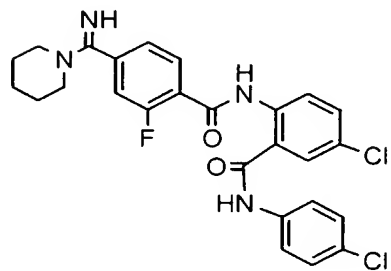
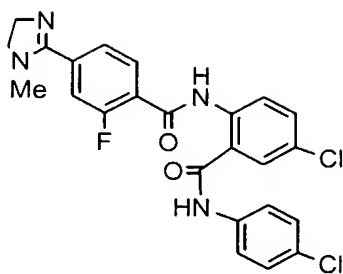
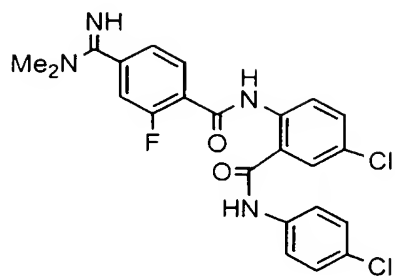
A still further embodiment of the present invention provides an individual compound which is a member selected from the following structures:

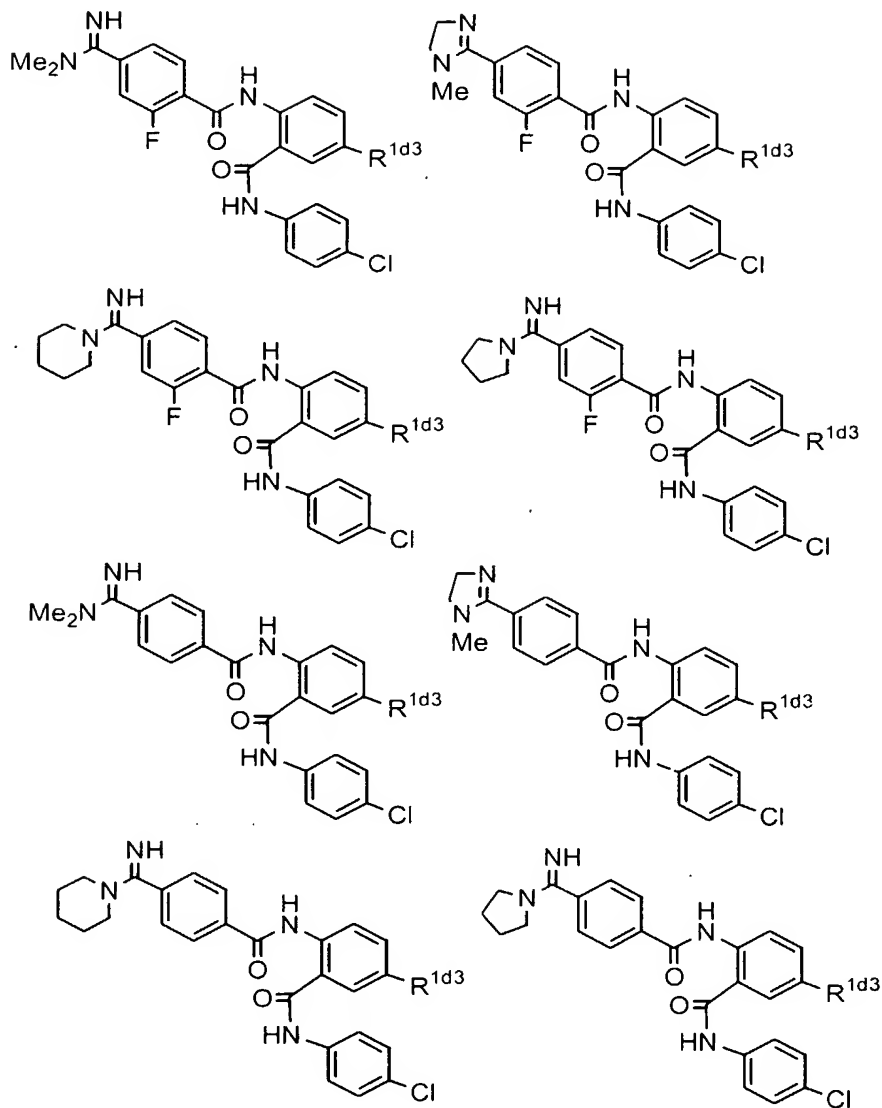


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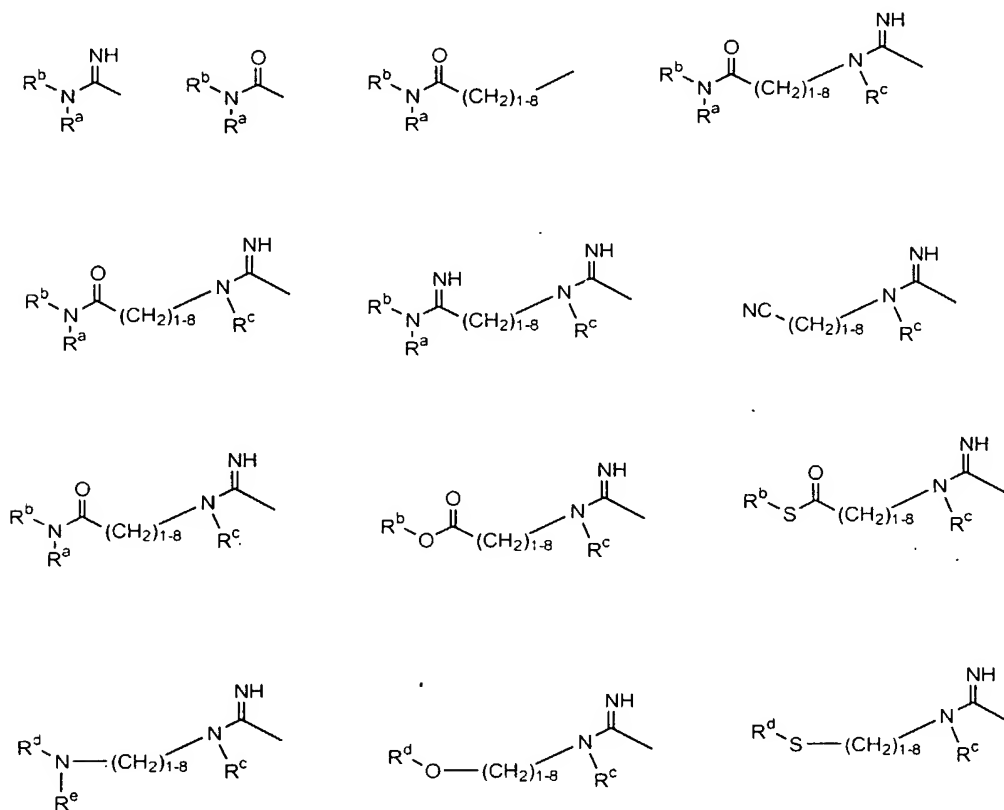
wherein

R^{ld3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OCF₃, -OCF₂H, and -OCF₂H,

- 5 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of the present invention provides compounds according to the invention as illustrated herein, wherein the A-Q- substituent is an amidinosubstituent, the amine portion of which is a cyclized amine heterocyclic ring, preferably a saturated cyclized amine heterocyclic ring, and the cyclized amine ring is substituted by 1-3 members. Examples of such A-Q substituents include but are not limited to:



- 10 wherein each of R^a , R^b , R^c , R^d and R^e is independently a member selected from the group consisting of C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_1 - C_8 acyl and C_1 - C_8 acyl C_1 - C_8 alkyl ester, and the R^a and R^b groups together with the nitrogen atom to which they are both attached may be cyclized to form a C_3 - C_8 heterocyclic ring having from 1 to 4 additional hetero ring atoms selected from O, N and S,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment is an embodiment wherein the amidino groups illustrated above as substituents for the cyclized amine heterocyclic ring are instead
5 form an acyclic amidino A-Q group and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Such compounds are formed by reacting the appropriate acyclic amine or cyclicized amine with an amidino group or with a thioimino group wherein the
10 remainder of the structures D-E-G-J-X are defined as in formula I or as in a preferred D-E-G-J-X structure illustrated in a preferred embodiment herein. Other ways to produce such compound structures will be apparent to an ordinary practitioner in this field upon consideration of the description herein and the illustrated preferred
embodiments.

15

This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives of the preferred compounds. In addition, the preferred compounds can exist in various isomeric and tautomeric forms,
20 and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or
25 converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative.

Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as
5 therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep
10 venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary
15 embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a
20 therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous
25 vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

5 The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, 10 including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used 15 and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

20 The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

25 Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into 30 shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal

efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other
5 factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in
10 sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and
15 other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose
20 or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for
25 therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of
30 certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection,

other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

5 Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic
10 needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective
15 dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

20 The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

25 Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable
30 dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

15

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are
5 incorporated herein by reference.

Compounds according to the invention can be synthesized utilizing procedures well known in the art. The reaction products are isolated and purified by conventional
10 methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or
15 converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

20 A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by
25 evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically
30 utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as

tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The
5 dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

10

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for
15 therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less
20 than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar
25 alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by
30 filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as

an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a
5 container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual
10 determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be
15 individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically,
20 applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from
25 about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of
30 this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder,

preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

5 Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above
10 materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty
15 vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

 In practicing the methods of this invention, the compounds of this invention
20 may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet
25 aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

30 The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of

coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

5

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

10

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

15

20

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary

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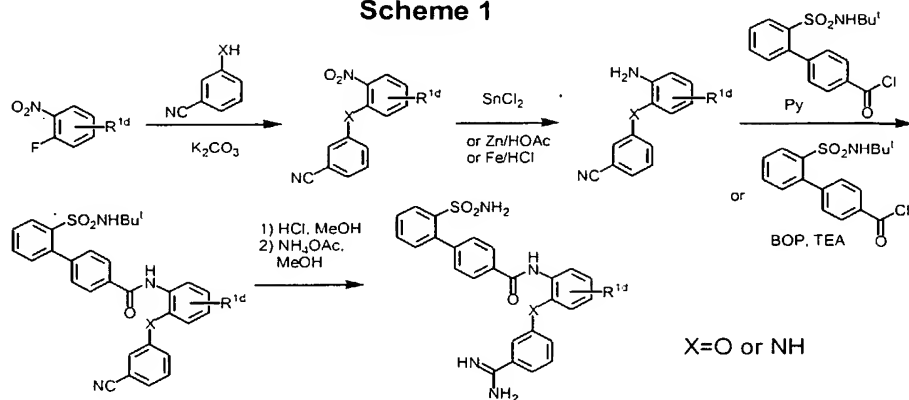
embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

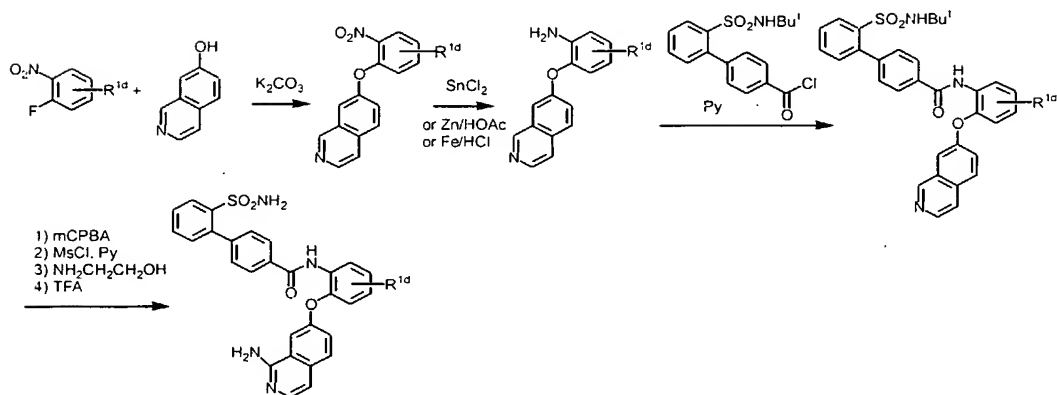
Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

EXAMPLES

Examples of Chemical Production Process General Reaction Schemes

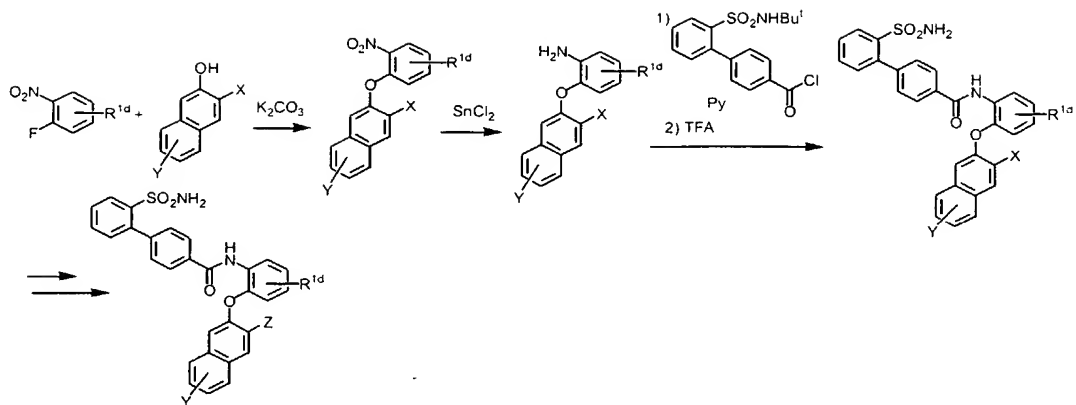
Scheme 1

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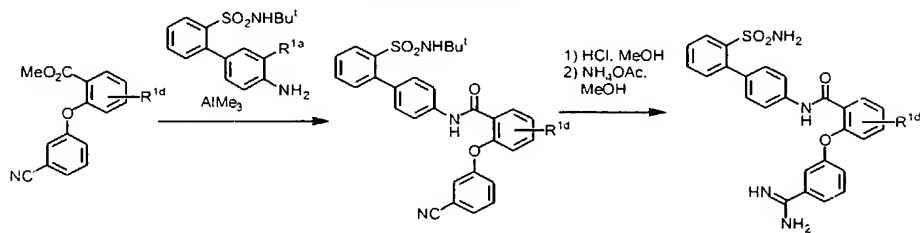
Scheme 2

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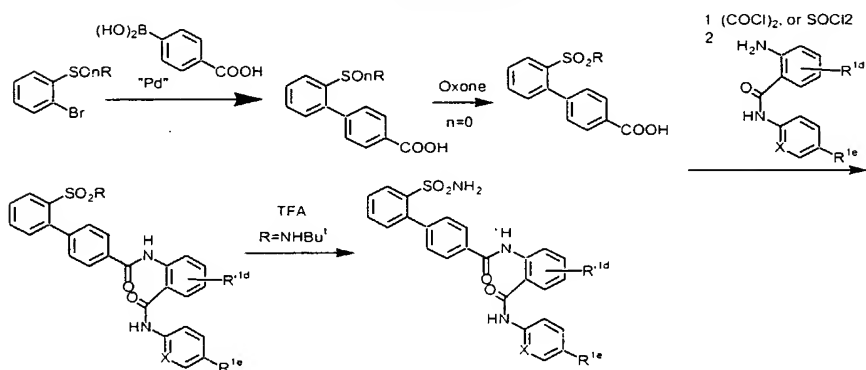
Scheme 3



Scheme 4

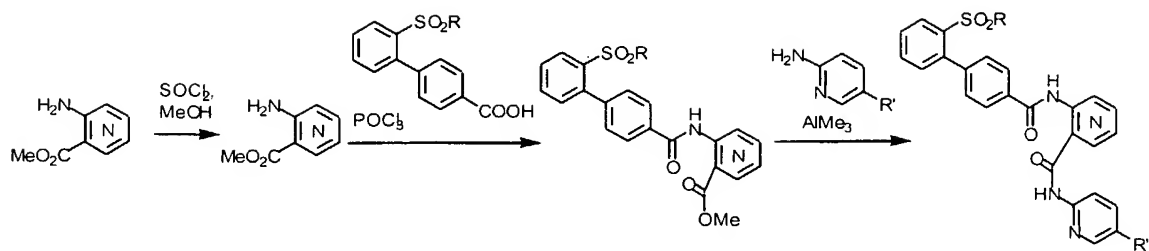


Scheme 5

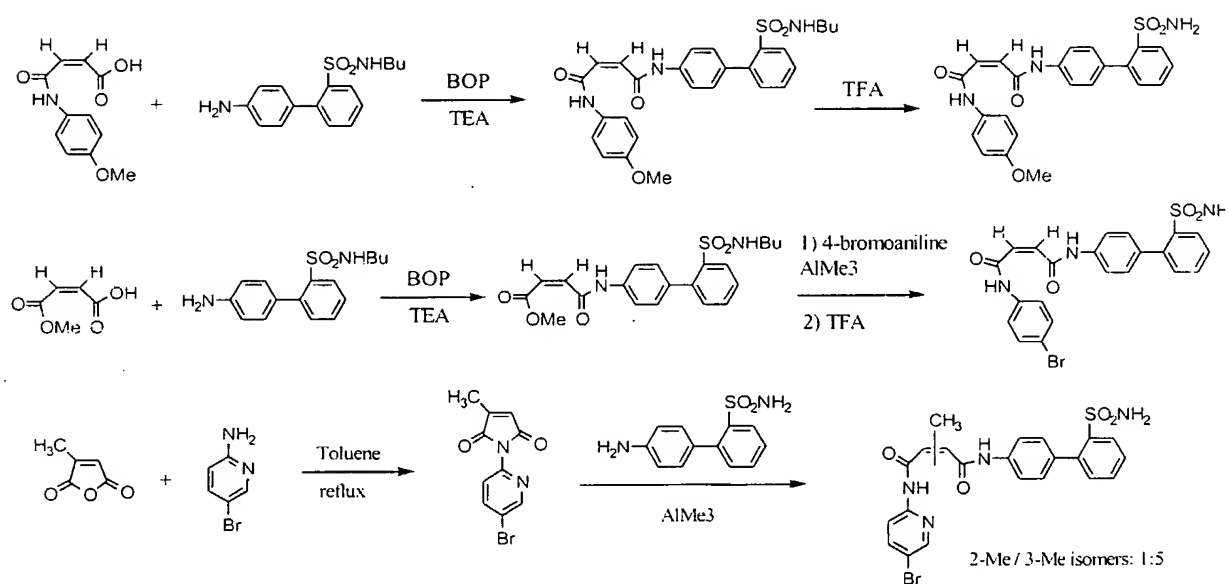


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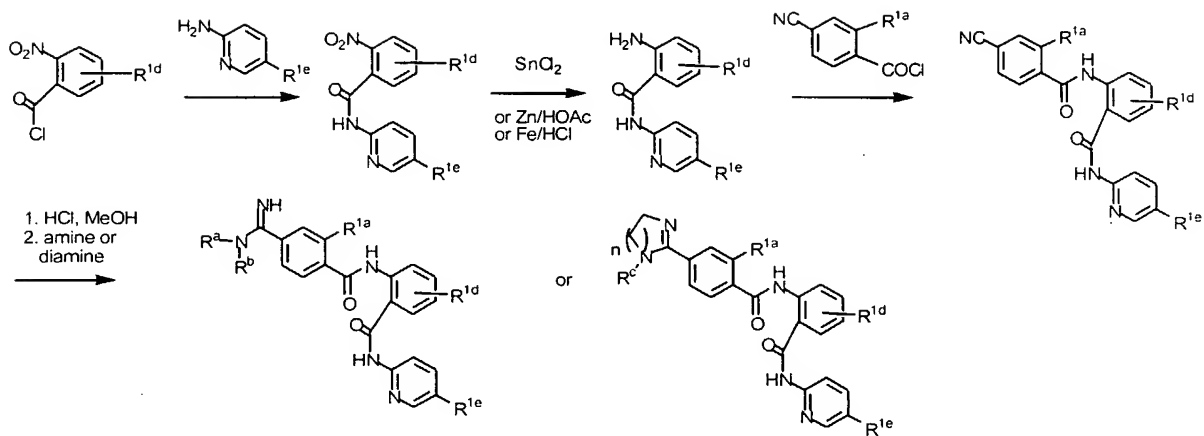
Scheme 6



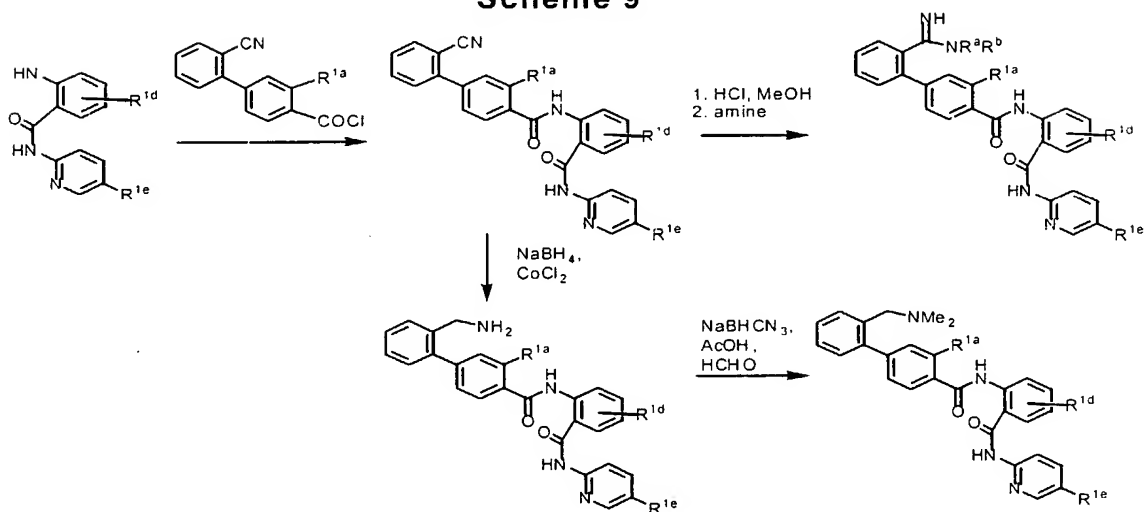
Scheme 7



Scheme 8

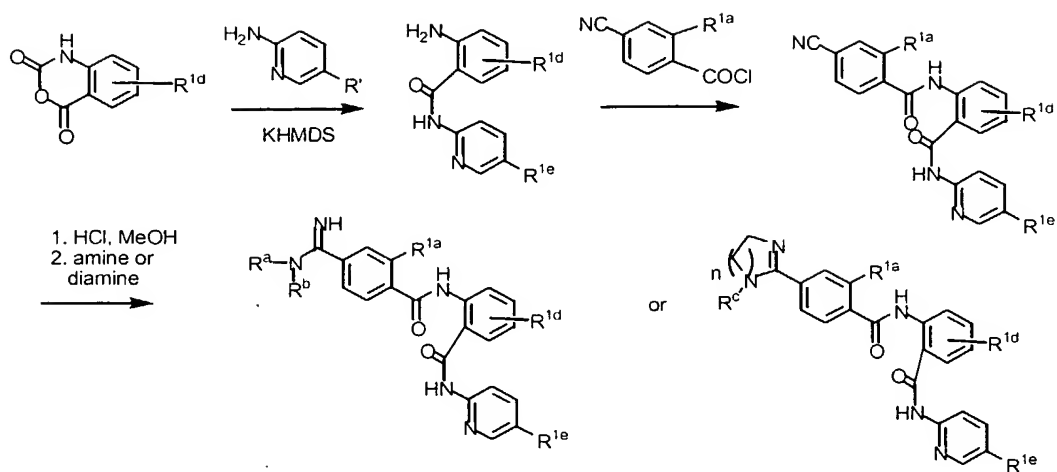


Scheme 9

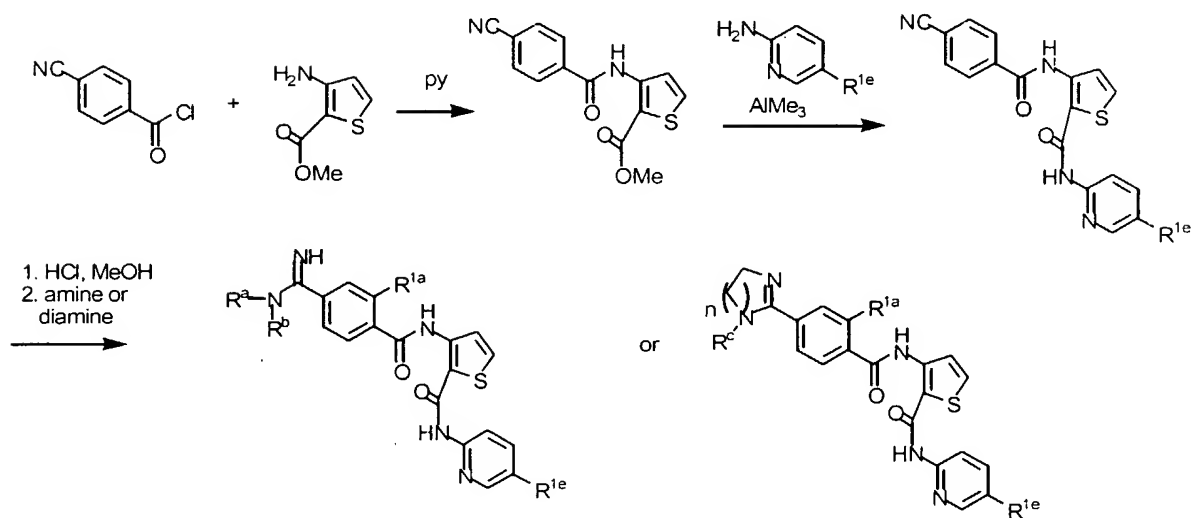


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Scheme 10

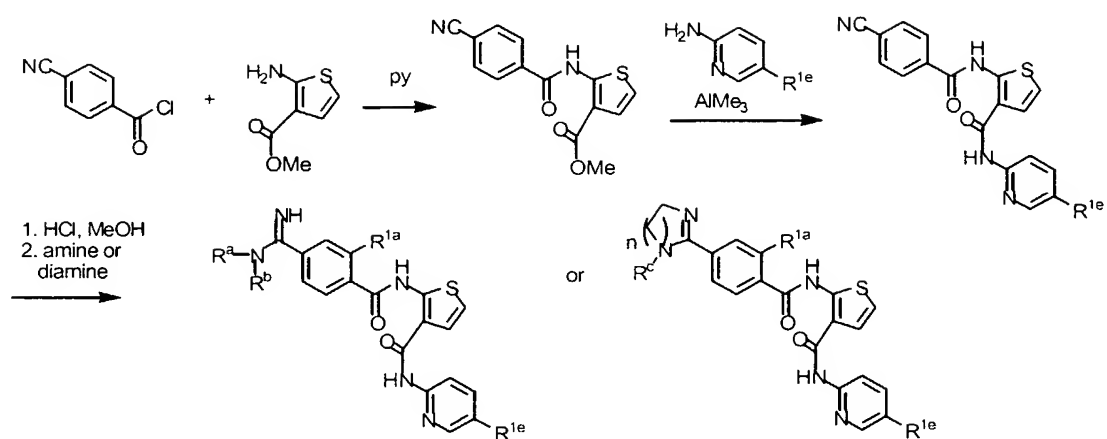


Scheme 11

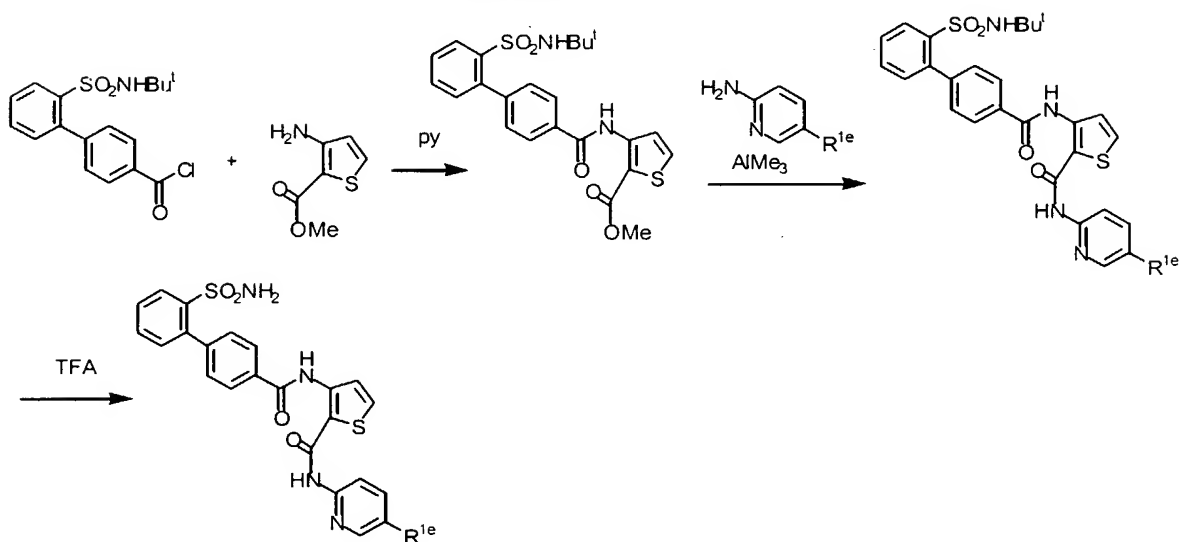


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Scheme 12



Scheme 13

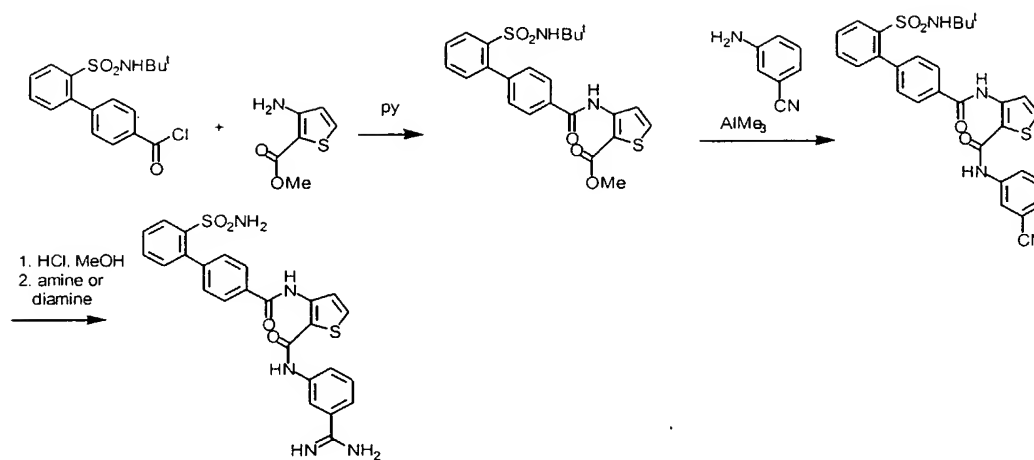


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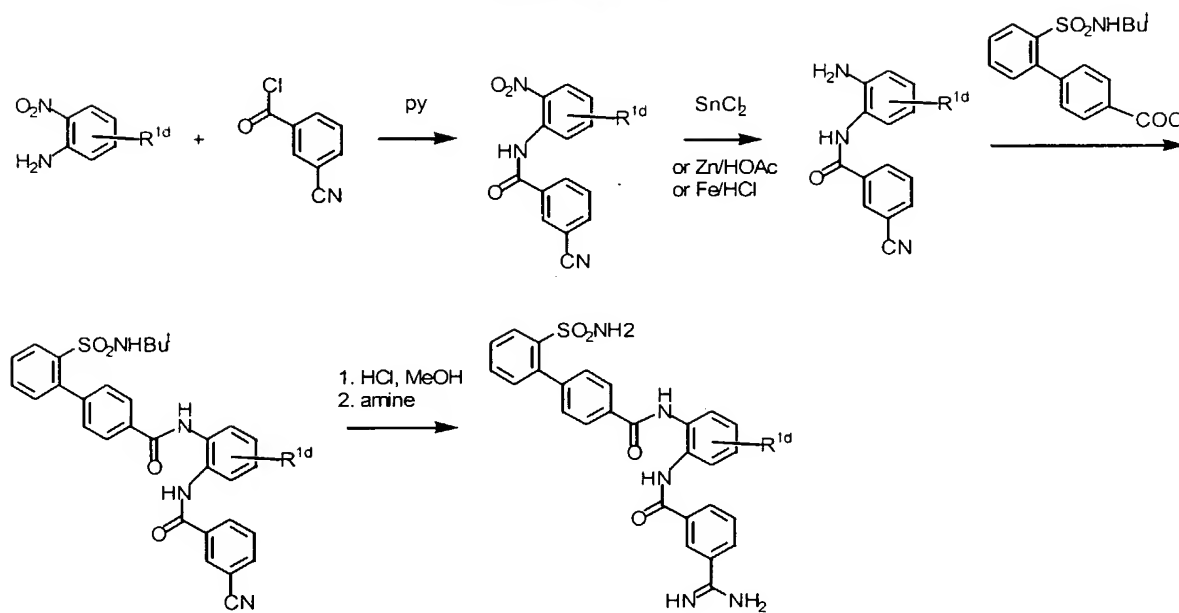
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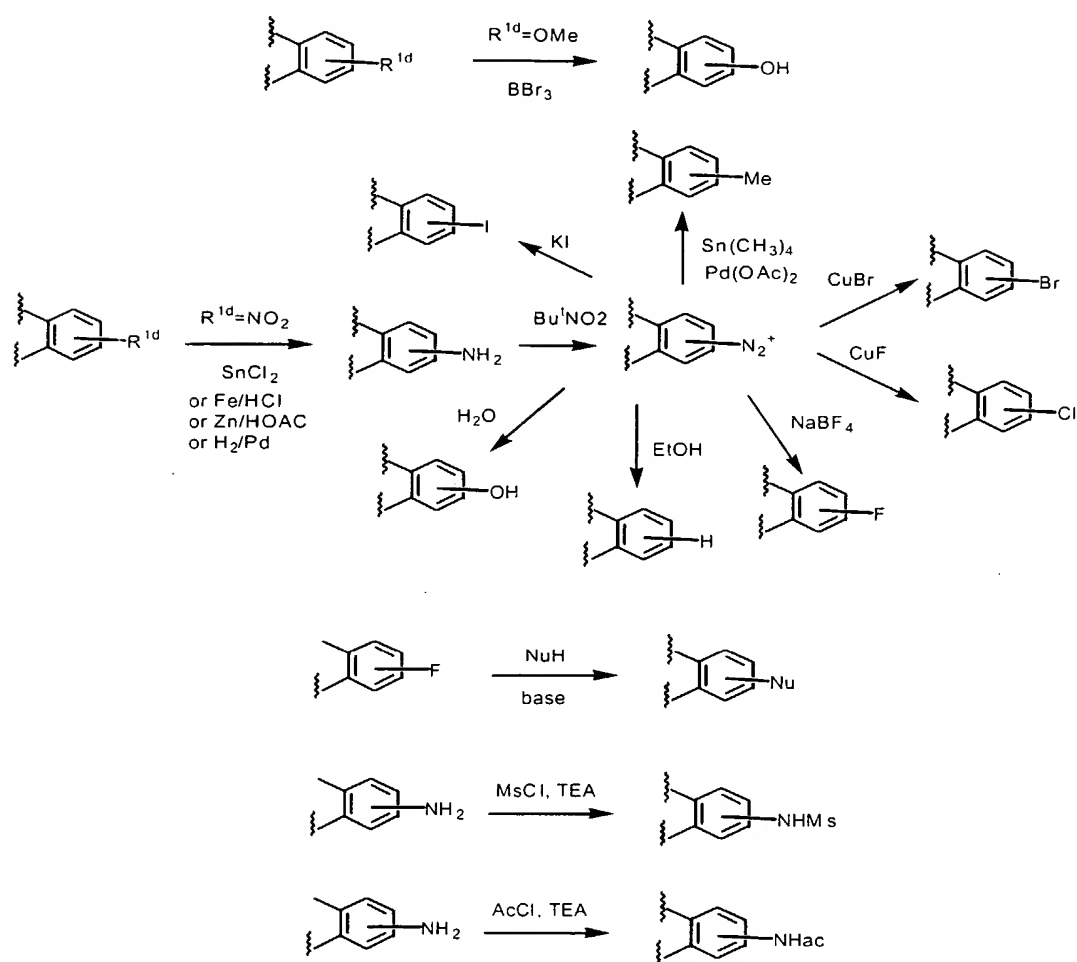
Scheme 14



Scheme 15

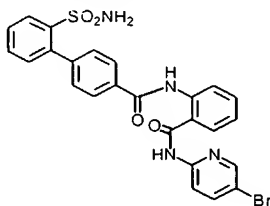


Scheme 16: Transformations of R^{1d}



Example 1

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



5 Step 1: A solution of 2-nitrobenzoyl chloride (3.70 g, 20 mmol, 1.0 equiv), 2-amino-5-bromopyridine (3.50 g, 1.0 equiv), pyridine (10 mL) in 25 mL of methylene chloride was stirred overnight. The volatile was evaporated, flash chromatography on silica gel gave N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (5.02 g, 77%). MS found for $C_{12}H_9BrN_3O_3$ ($M+H$)⁺: 322.

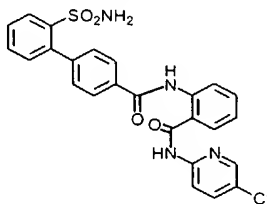
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Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (1.0 g, 3.1 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_2 \cdot 2H_2O$ (2.80 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer
15 was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (0.89 g, 98%). MS found for $C_{12}H_{11}BrN_3O$ ($M+H$)⁺: 292.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight,
20 washed with H_2O . The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (470 mg, 85%). MS
25 found for $C_{25}H_{20}BrN_4O_4S$ ($M+H$)⁺: 551.

Example 2

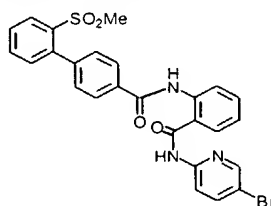
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



- 5 A mixture of N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (247 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and
- 10 HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (370 mg, 73%). MS found for C₂₅H₂₀ClN₄O₄S (M+H)⁺: 507.

15 Example 3

N-(5-bromo-2-pyridinyl)-(2-4-[(2-methylsulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



- Step 1: To a mixture of 2-bromothioanisole (4.8g, 23.6mmol), 4-
- 20 carboxybenzeneboronic acid (3.92g, 23.6mmol) and 2M K₂CO₃ (35.5mmol, 71mmol) in dioxane (20ml) was added dichlorobis(triphenylphosphine)palladium (II) (415mg, 0.6mmol) under Ar. It was refluxed for 2hrs. After the removal of the solvent, the residue was neutralized by 1N HCl and extracted with dichloromethane. The organic

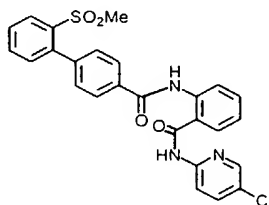
layer was dried over MgSO_4 and concentrated *in vacuo* to give 4-[(2-methylthio)phenyl]benzoic acid (5.9g, 100%). ES-MS $(\text{M}+\text{H})^+=245$.

Step 2: To a solution of 4-[(2-methylthio)phenyl]benzoic acid (3.43g, 14mmol) in
5 H_2O (10ml) and acetone (20ml) was added oxone monopersulfate (34.6g, 56mmol). The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was dried over MgSO_4 and concentrated *in vacuo* to give 2.16g (63%) 4-[(2-methylsulfonyl)phenyl]benzoic acid. ES-MS $(\text{M}+\text{H})^+=277$.

10 Step 3: To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (552mg, 2mmol) in dichloromethane (5ml) was added oxalyl chloride (350ul, 4mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-bromo-2-pyridinyl)-
15 (2-amino)phenylcarboxamide (700mg, 2.4mmol), pyridine (486ul, 6mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 414mg (38%) of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-
20 methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS $\text{M}^+=550$, $(\text{M}+2)^+=552$.

Example 4

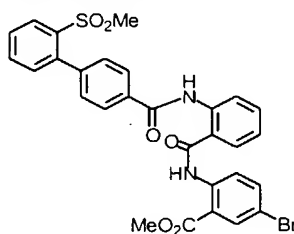
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-
25 methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol) in dichloromethane (5ml) was added oxalyl chloride (175 μ l, 2 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-chloro-2-pyridinyl)-
 5 (2-amino)phenylcarboxamide (297mg, 1.2 mmol), pyridine (243 μ l, 3 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 95 mg (20%) of N-(5-chloro-2-pyridinyl)-(2-(4-[(2-
 10 methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS $M^+ = 505.5$, $(M+2)^+ = 507.5$.

Example 5

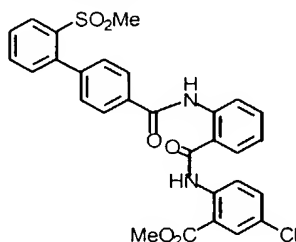
**N-(4-bromo-2-methoxycarbonylphenyl)-(2-(4-[(2-
 15 methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.**



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was
 20 dissolved in 5 mL of dichloromethane, N-(4-bromo-2-methoxycarbonylphenyl)-(2-amino)phenylcarboxamide (348 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 480 mg (79%) of N-(4-bromo-2-methoxycarbonylphenyl)-(2-(4-[(2-
 25 methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}BrN_2O_6S$ $(M+H)^+$: 607.

Example 6

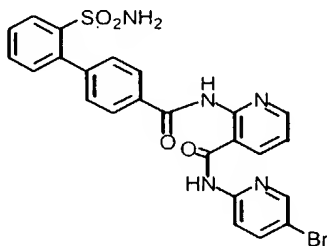
N-(4-chloro-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



- 5 A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-chloro-2-methoxycarbonylphenyl)-(2-amino)phenylcarboxamide (304 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was
- 10 purified by flash column to give 479 mg (85%) of N-(4-chloro-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}ClN_2O_6S$ ($M+H$)⁺: 563.

15 Example 7

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



- Step 1: A solution of 2-aminopyridine-3-carboxylic acid (138 mg, 1 mmol) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid and $POCl_3$. The
- 20

resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over MgSO_4 , filtered and flash chromatographed to give methyl 2-(4-[(2-t-

butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (243 mg,

5 52%). MS found for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_5\text{S}$ ($\text{M}+\text{H}$)⁺: 468.

Step 2: To A solution of 2-amino-5-bromopyridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-

10 butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg,

0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with

saturated aqueous potassium sodium tartrate. The organic layer was dried over

MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min.

TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in

15 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-

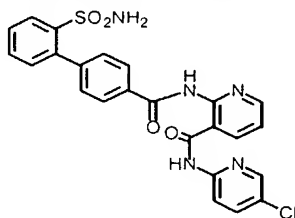
aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (17 mg, 48%).

MS found for $\text{C}_{24}\text{H}_{19}\text{BrN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 552.

Example 8

20 N-(5-chloro-2-pyridinyl)-(2-4-[(2-

aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



To A solution of 2-amino-5-chloropyridine (32 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added

25 methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-

carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight,

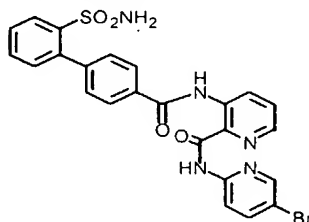
quenched with saturated aqueous potassium sodium tartrate. The organic layer was

dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (21 mg, 66%).

5 MS found for $\text{C}_{24}\text{H}_{19}\text{ClN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 508.

Example 9

N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide.



10

To A solution of 2-amino-5-bromopyridine (69.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated

15 aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-bromo-2-pyridinyl)-(3-4-[(2-

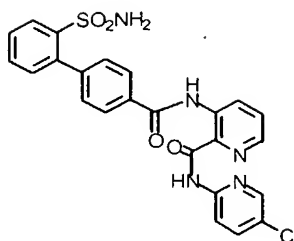
aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide (29 mg, 53%).

20 MS found for $\text{C}_{24}\text{H}_{19}\text{BrN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 552.

Example 10

N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.

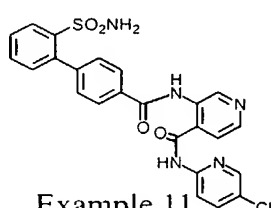
167



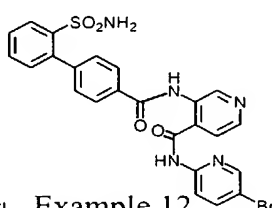
To A solution of 2-amino-5-chloropyridine (51.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 1 mL, 20 equiv) for 30-min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 0.1mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (33 mg, 64%). MS found for $\text{C}_{24}\text{H}_{19}\text{ClN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 508.

Examples 11-14

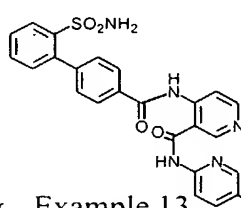
The following compounds were prepared using the procedure described previously:



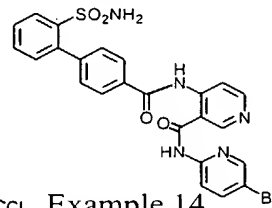
Example 11
MS ($\text{M}+\text{H}$): 508



Example 12
MS ($\text{M}+\text{H}$): 552



Example 13
MS ($\text{M}+\text{H}$): 508

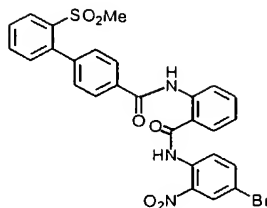


Example 14
MS ($\text{M}+\text{H}$): 552

Example 15

N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

168

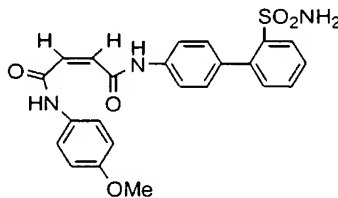


Step 1: A mixture of methyl 2-aminobenzoate (150 mg, 1 mmol, 1.0 equiv), 4-[(2-methylsulfonyl)phenyl]benzoic chloride (294 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer
 5 was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarboxyl)aminobenzoate (250 mg, 54%). MS found for C₂₅H₂₇N₂O₅S (M+H)⁺: 467.

Step 2: To a solution of 4-bromo-2-nitroaniline (43.4 mg, 0.2 mmol, 2.0 equiv) in 5
 10 mL of methylene chloride treated with AlMe₃ (2M in hexane, 0.3 mL, 6 equiv) for 30 min was added methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarboxyl)aminobenzoate (46.6 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave N-(4-bromo-2-nitrophenyl)-
 15 (2-(4-[(2-methylsulfonyl)phenyl]phenylcarboxyl)amino)phenylcarboxamide (5 mg, 9%). MS found for C₂₇H₂₁BrN₃O₆S (M+H)⁺: 594.

Example 16

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



20

A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide.

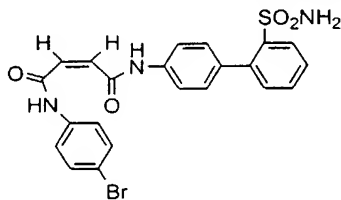
To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H₂O, then with 5% NaHCO₃, dried over Na₂SO₄, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH₃CN in H₂O (containing 0.1% TFA) to 100% CH₃CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M + H).

B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide (40 mg, 79 μmol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH₃CN in H₂O (containing 0.1% TFA) to 95% CH₃CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M + H) and 474 (M + Na). ¹H NMR (CDCl₃) δ 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz), 7.60 – 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 17

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)maleamic methyl ester.

To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH₂Cl₂ (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH₂Cl₂ solution was then washed with sat. NaHCO₃, 1N HCl and sat. NaCl. The solution was dried over Na₂SO₄, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M + H - ^tBu) and 439 (M + Na).

10

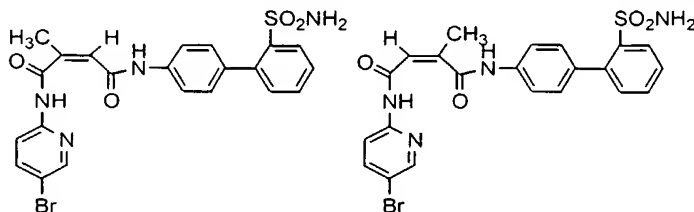
B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH₂Cl₂ (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH₂Cl₂ were added, and organic phase was separated, dried over Na₂SO₄, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH₃CN in H₂O (containing 0.1% TFA) to 95% CH₃CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M + H), 522 and 524 (M + Na). ¹H NMR (CD₃OD) δ 8.09 (d, 1H, J = 8 Hz), 7.68 (d, 2H, J = 8 Hz), 7.64 – 7.28 (m, 9H), 6.45 (AB type, 2H).

25

Examples 18 and 19

Preparation of N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.



5

A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M + H).

10

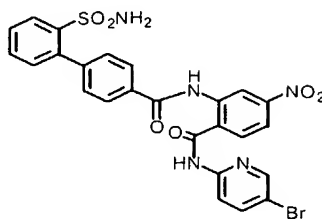
B. Preparation of N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

15

To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH₂Cl₂ (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH₂Cl₂ (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1 : 5. MS 515 and 517 (M + H), 537 and 539 (M + Na).

20

25

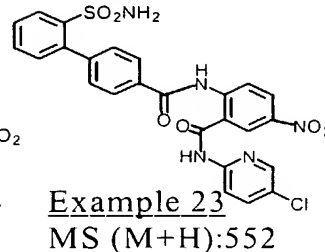
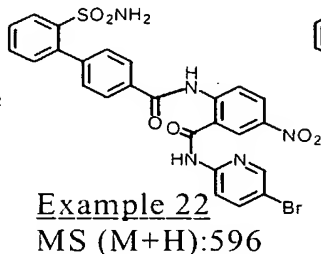
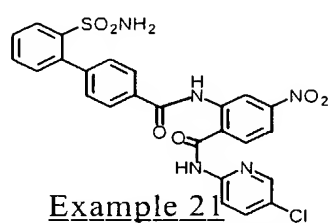
Example 20**N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide.**

- 5 Step 1: A solution of 2-amino-4-nitrobenzoic acid (182 mg, 1 mmol, 1 equiv) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv) and POCl₃ (0.93 mL, 10 equiv). The resulting mixture was stirred at rt
- 10 overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and flash chromatographed to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (430 mg, 84%). MS found for C₂₅H₂₆N₃O₇S (M+H)⁺: 512.
- 15 Step 2: To A solution of 2-amino-5-bromopyridine (135 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe₃ (2M in hexane, 1 mL, 10 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (100 mg, 0.2 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was
- 20 dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide (42 mg, 36%). MS found for C₂₅H₁₉BrN₅O₆S (M+H)⁺: 596.

25

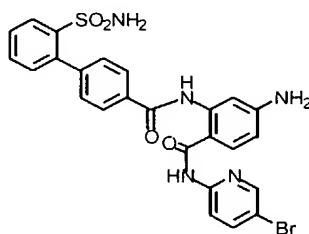
Examples 21-23

The following compounds were prepared according to the procedure described previously:



5 Example 24

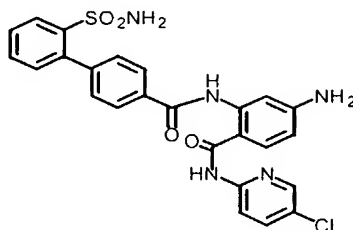
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.



- 10 A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-nitrophenylcarboxamide (65 mg, 0.1 mmol, 1 equiv) in 10 mL of EtOAc was treated with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (90 mg, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous NaHCO_3 and 1N NaOH. The organic layer was dried over MgSO_4 ,
 15 filtered and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide, which was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide (47 mg,
 20 84%). MS found for $\text{C}_{25}\text{H}_{21}\text{BrN}_5\text{O}_4\text{S}$ (M+H)⁺: 566.

Example 25

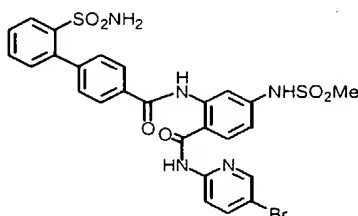
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.



- 5 This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ ($M+H$)⁺: 522.

Example 26

- 10 **N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.**

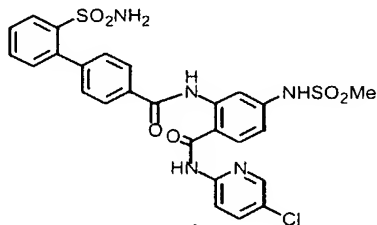


- A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide (62 mg, 0.1mmol, 1 equiv) in 3 mL of CH_2Cl_2 was treated with $MsCl$ (23 mg, 2 equiv) and TEA (0.5 mL) at rt for 4 h. The mixture was washed with water and dried over $MgSO_4$, filtered and evaporated. The residue was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide (33 mg, 52%). MS found for $C_{26}H_{23}BrN_5O_6S_2$ ($M+H$)⁺: 644.

Example 27

175

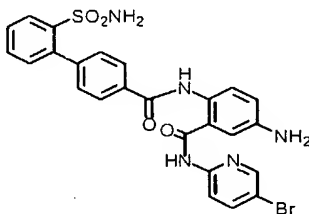
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.



This compound was prepared according to the procedure described in example 53. MS
5 found for $C_{26}H_{23}ClN_5O_6S_2$ ($M+H$)⁺: 600.

Example 28

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.

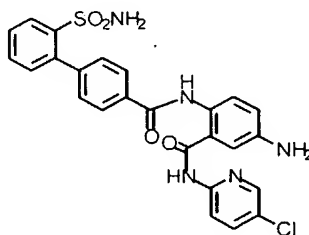


10

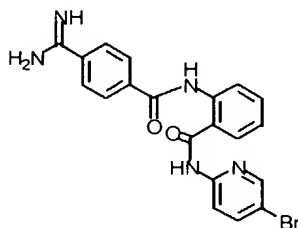
This compound was prepared according to the procedure described in example 50. MS
found for $C_{25}H_{21}BrN_5O_4S$ ($M+H$)⁺: 566.

Example 29

15 **N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.**



This compound was prepared according to the procedure described in example 50. MS
found for $C_{25}H_{21}ClN_5O_4S$ ($M+H$)⁺: 522.

Example 30**N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide.**

5

Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-cyano benzoyl chloride (165 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (349 mg, 70%). MS found for C₂₀H₁₄BrN₄O₂ (M+H)⁺: 421.

10

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg) in 10 mL methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide (31 mg, 70%). MS found for C₂₀H₁₇BrN₅O₂ (M+H)⁺: 438.

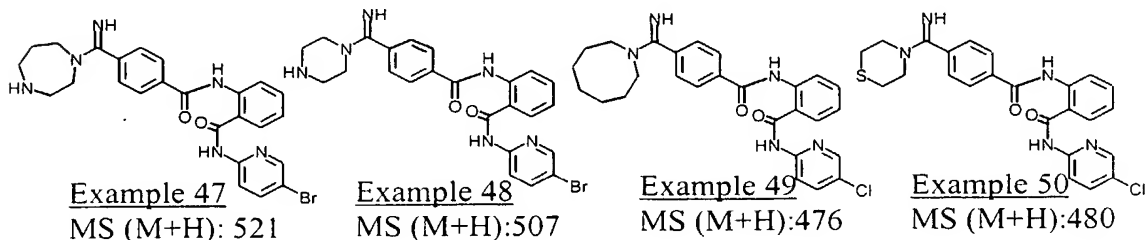
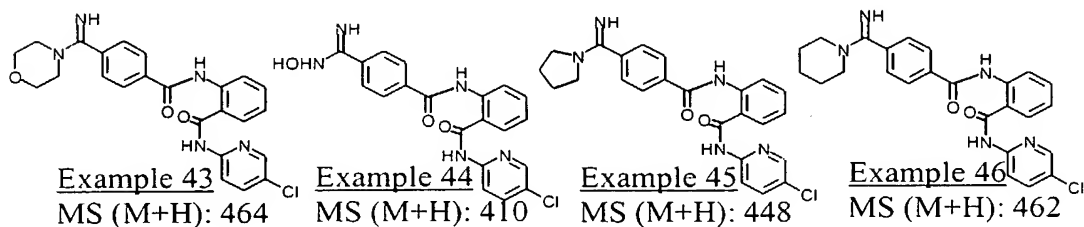
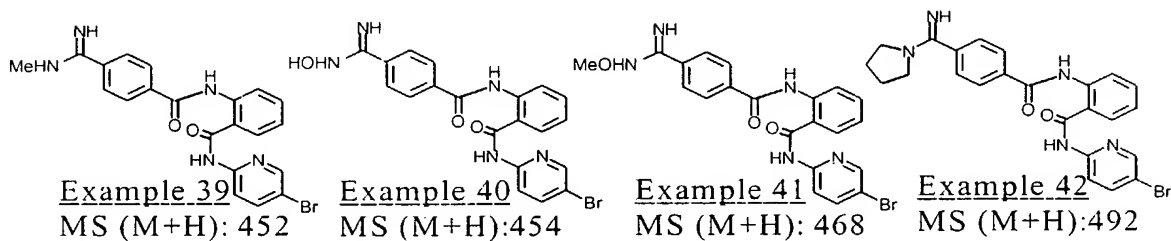
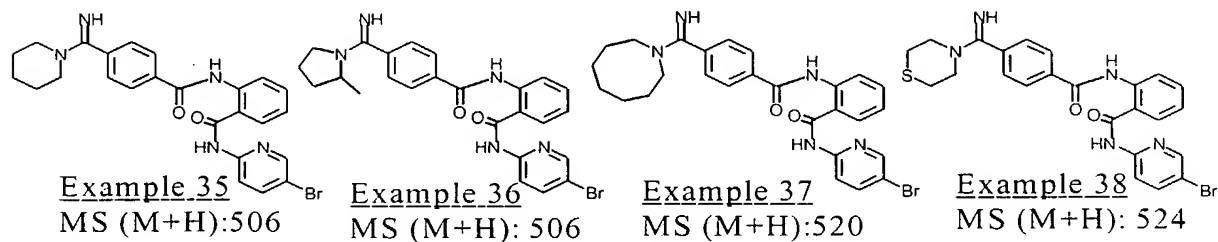
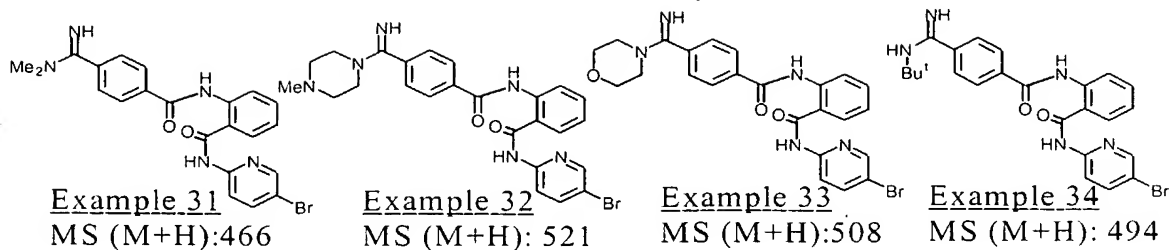
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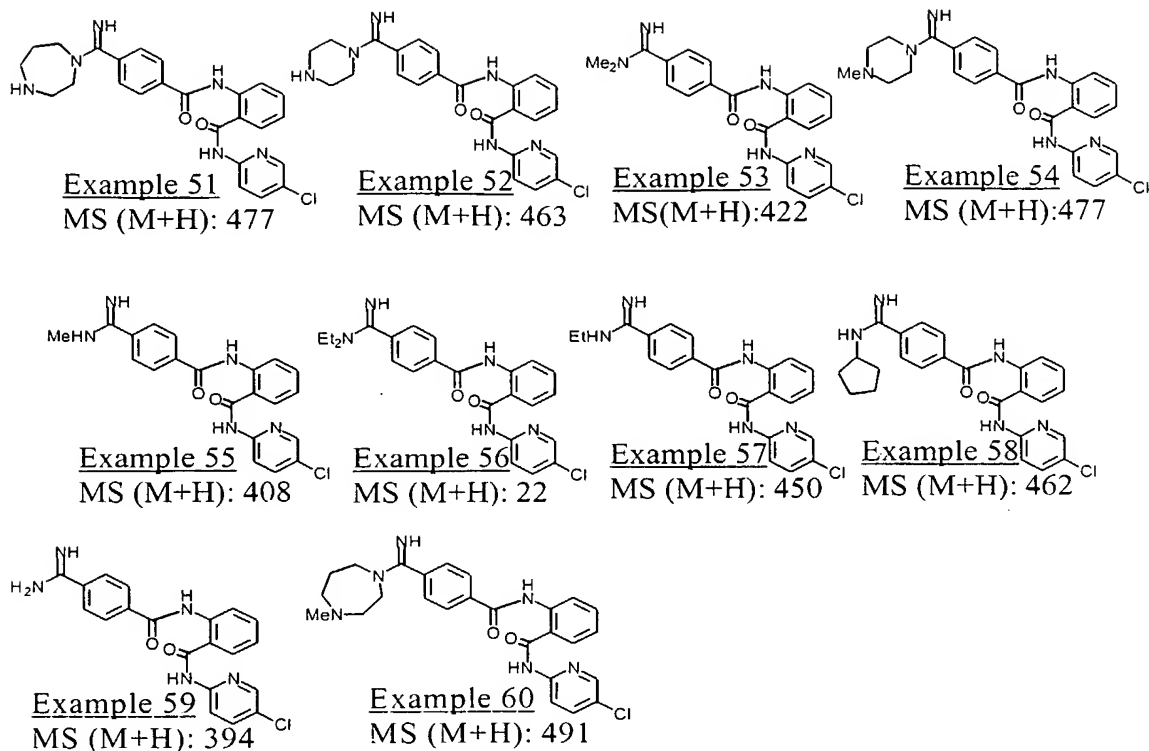
20

Examples 31-60

The following compounds were prepared according to the procedure described previously

25

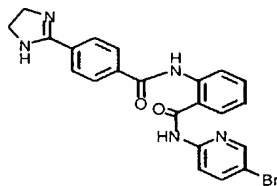




5

Example 61

N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazoliny)phenylcarbonyl)amino)-phenylcarboxamide.

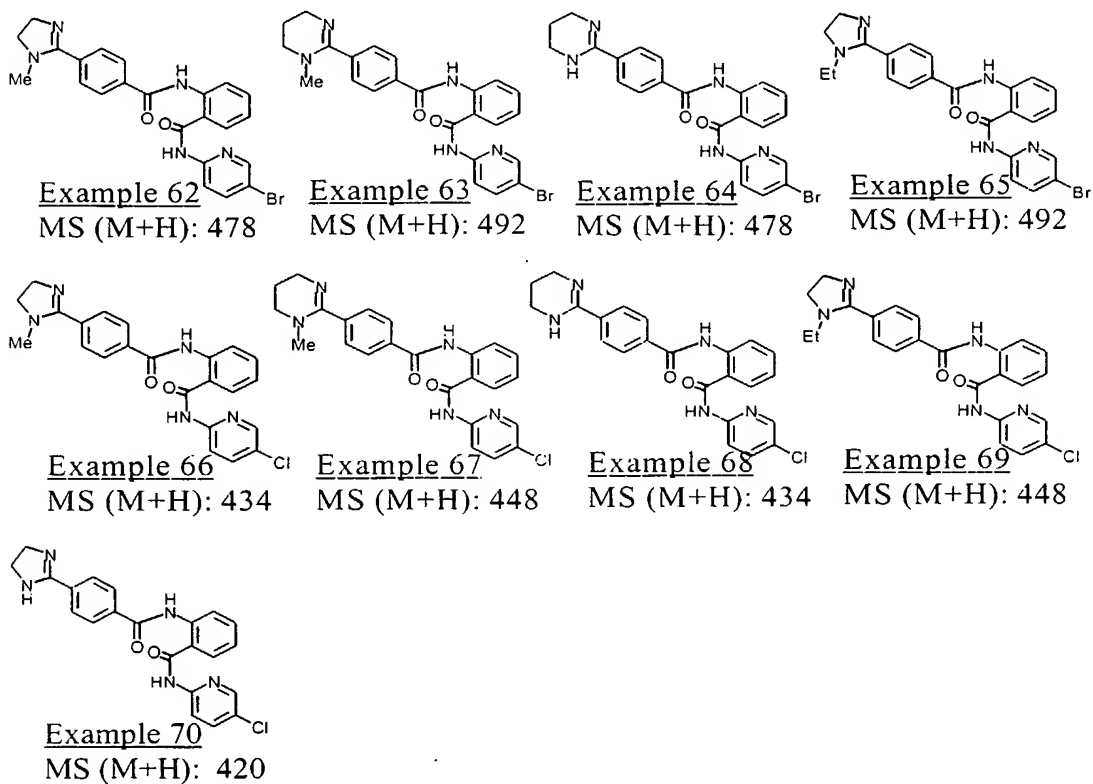


- 10 A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-
 (2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of
 methanol until saturation. The mixture was stirred at rt overnight and evaporated. The
 resulting residue was treated with ethylene diamine (40 mg) in 10 ml methanol at
 reflux temperature for 2 h. The solvent was removed at reduced pressure and the
 15 crude benzimidine was purified by HPLC (C18 reversed phase) eluting with 0.5%
 TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(2-

imidazolyl)phenylcarbonyl)amino)-phenylcarboxamide (41 mg, 89%). MS found for $C_{22}H_{19}BrN_5O_2$ (M+H)⁺: 464.

Examples 62-70

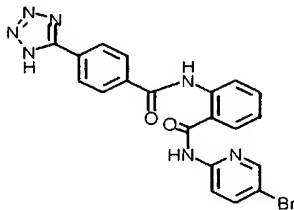
- 5 The following compounds were prepared according to the procedure previously described



10

Example 71

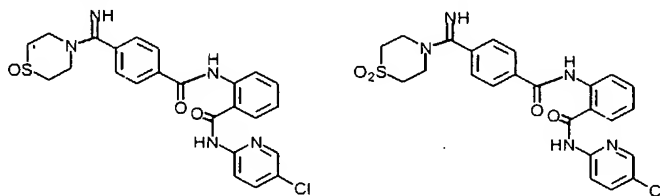
N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide.



A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) and sodium azide (67 mg, 10 equiv) in 5 mL of DMF was heated at 100°C for 24h. The reaction mixture was diluted with EtOAc, washed with water, dried, filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide (33 mg, 65%). MS found for C₂₀H₁₅BrN₇O₂ (M+H)⁺: 464.

Example 72 and Example 73

N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl)]iminimethy]phenylcarbonyl)amino)-phenylcarboxamide and **N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl)]iminimethy]phenylcarbonyl)amino)-phenylcarboxamide**.

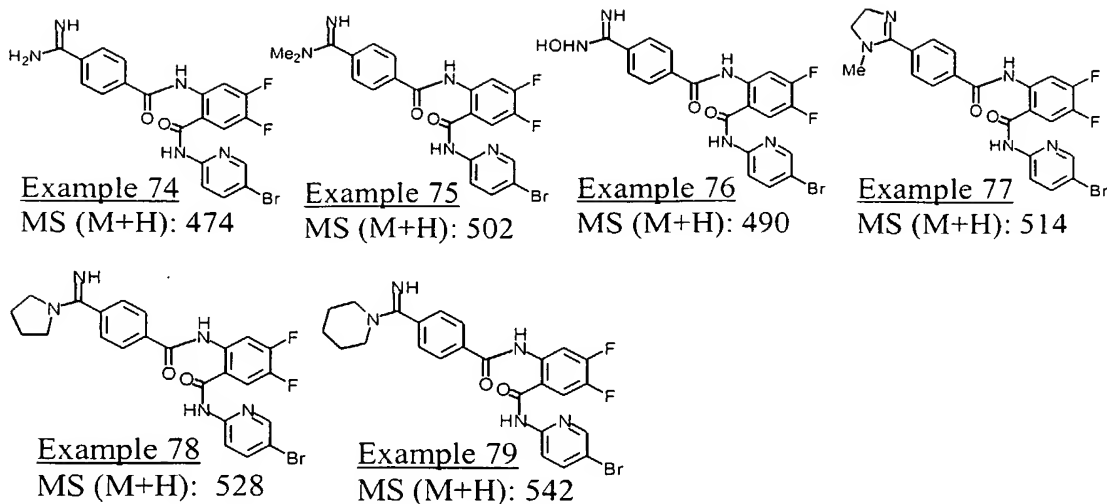


A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-(1,4-thiazaperhydroin-4-yl)iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (48 mg, 0.1 mmol) and 3 mL of 30% hydrogen doxide was stirred at rt for 12h. The reaction was quenched with solid Na₂S₂O₃. Purification by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl)]iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (15 mg, 31%), MS found for C₂₄H₂₃ClN₅O₄S (M+H)⁺: 512 and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl)]iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (20 mg, 41%). MS found for C₂₄H₂₃ClN₅O₃S (M+H)⁺: 496.

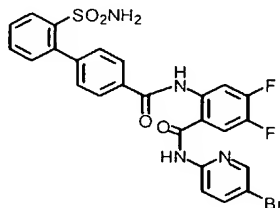
Examples 74-79

The following compounds were prepared according to the procedure previously described

181

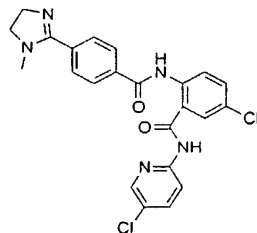
Example 80

- 5 **N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarboxylamino)-4,5-difluorophenylcarboxamide.**



This compound was prepared according to the procedure previously described. MS found for $C_{25}H_{18}BrF_2N_4O_4S$ (M+H)⁺: 587.

10

Example 81

- Step 1: To a solution of 2-amino-5-chloropyridine (328mg, 2.55mmol) in tetrahydrofuran (5ml) was 0.5M potassium bis(trimethylsilyl)amide in toluene (10ml, 15 5.05mmol) dropwise at $-78^{\circ}C$. After stirred for additional 0.5hr at $-78^{\circ}C$, the

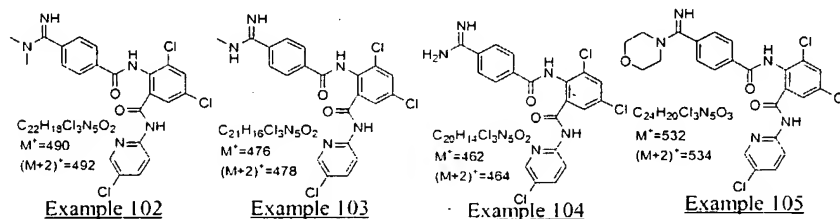
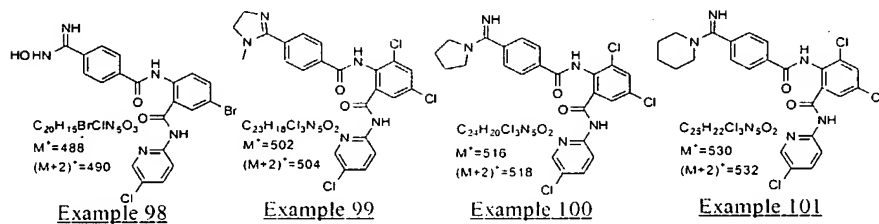
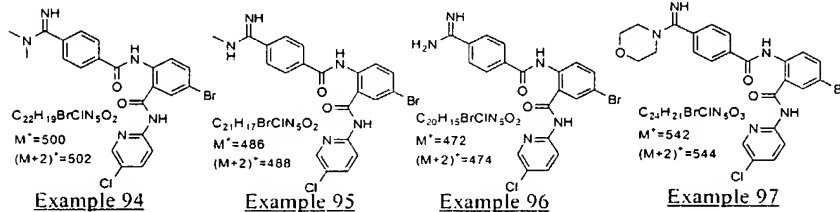
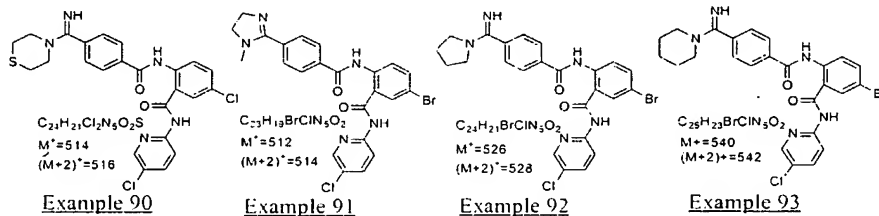
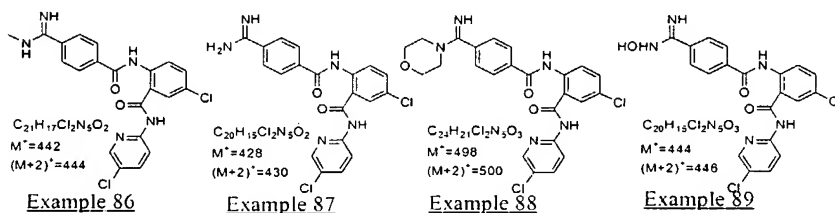
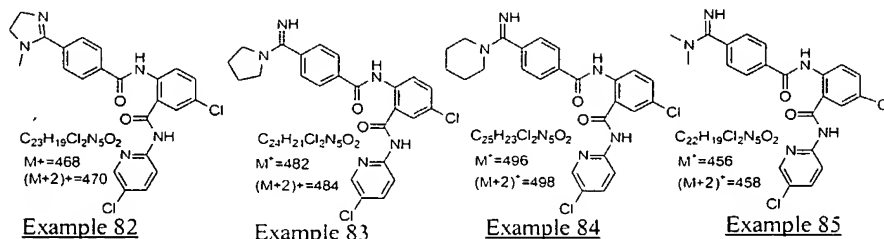
mixture was added 5-chloroisatoic anhydride (0.5g, 2.55mmol) at -78°C . The mixture was warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 100%). MS found for $\text{C}_{12}\text{H}_9\text{Cl}_2\text{N}_3\text{O}$ $\text{M}^+=282$, $(\text{M}+2)^+=284$.

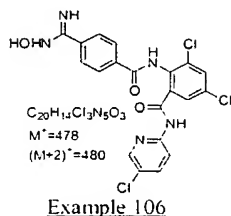
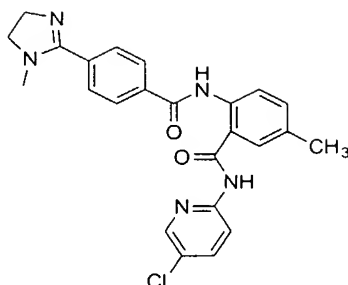
Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 2.52mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (417mg, 2.52mmol) and pyridine (0.611ml, 7.55mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-cyanophenyl}carboxamide as a solid (683mg, 66%). MS found for $\text{C}_{20}\text{H}_{12}\text{Cl}_2\text{N}_4\text{O}_2$ $\text{M}^+=411$, $(\text{M}+2)^+=413$.

Step 3: To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-cyanophenyl}carboxamide (683mg, 1.66mmol) in anhydrous pyridine (10ml) and triethyl amine (1ml) was saturated with hydrogen sulfide gas at 0°C . The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous acetone (5ml) and iodomethane (1ml, 16.6mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the residue was dissolved in anhydrous methanol (5ml) and added a solution of N-methylethylenediamine (0.732ml, 8.3mmol) and acetic acid (1.5ml) in anhydrous methanol (5ml). The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for $\text{C}_{23}\text{H}_{19}\text{Cl}_2\text{N}_5\text{O}_2$ $\text{M}^+=468$ $(\text{M}+2)^+=470$.

Examples 82-106

The following compounds were prepared according to the procedure previously described



Example 107

- 5 Step 1: To a solution of 5-methyl-2-nitrobenzoic acid (1g, 5.52mmol) in dichloromethane (5ml) was added oxalyl chloride (0.964ml, 11.04mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-chloropyridine (852mg, 6.62mmol) and pyridine (1.34ml, 16.56mmol) were
- 10 added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide as a solid (1.48g, 92%). MS found for $C_{13}H_{10}ClN_3O_3$ $M^+ = 291$, $(M+2)^+ = 293$.

15

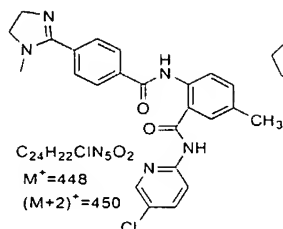
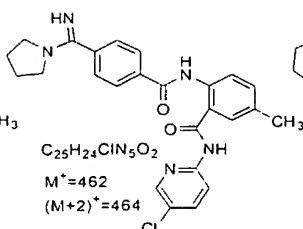
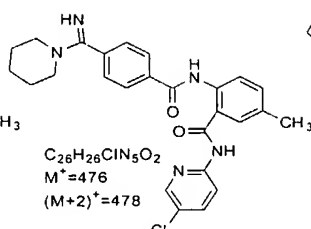
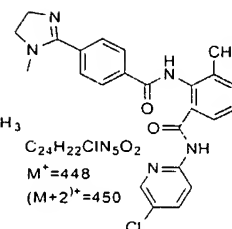
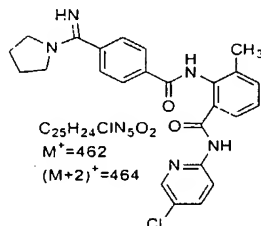
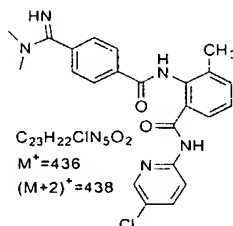
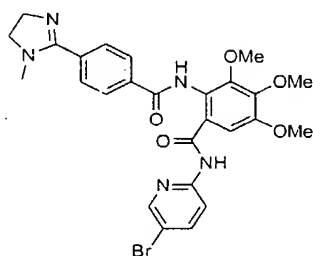
- Step 2: To a solution of the compound of N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide (1.48g, 5.1mmol) in methanol (10ml) was added 5% Pt/C (1.48g, 0.19mmol). The mixture was applied hydrogen balloon at r.t. for 2 hrs. After the filtration by Celite, the filtrate was concentrated to give (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 100%). MS found for $C_{13}H_{12}ClN_3O$ $M^+ = 262$, $(M+2)^+ = 264$.
- 20

- Step 3: To a solution of the compound of (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 5.2mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (860mg, 5.2mmol) and pyridine (1.26ml, 15.6mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide as a solid (830mg, 41%). MS found for $C_{21}H_{15}ClN_4O_2$ $M^+=390$, $(M+2)^+=392$.
10. Step 4: To a solution of the compound of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide (830mg, 2.1mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.926ml, 10.5mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for $C_{24}H_{22}ClN_5O_2$ $M^+=448$, $(M+2)^+=450$.

20

Examples 108-113

The following compounds were prepared according to the procedure previously described

Example 108Example 109Example 110Example 111Example 112Example 113Example 114

- 5 Step 1: To a solution of 3,4,5-trimethoxy-2-nitrobenzoic acid (0.5g, 1.95mmol) in dichloromethane (5ml) was added oxalyl chloride (0.34ml, 3.9mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-bromopyridine (0.81g, 4.7mmol) and pyridine (0.94ml, 11.7mmol) were added to the
- 10 solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide as a solid (790mg, 98%). MS found for $C_{15}H_{14}BrN_3O_6$ $M^+ = 412$, $(M+2)^+ = 414$.

15

Step 2: To a solution of the compound of N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide (790mg, 1.92mmol) in ethyl acetate (5ml) was added tin

chloride (II) hydrate (1.73g, 7.67mmol). The mixture was stirred under reflux condition for 2 hrs. After filtered by Celite, the filtrate was added 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570mg, 77%). MS found for C₁₅H₁₆BrN₃O₄ M⁺=382, (M+2)⁺=384.

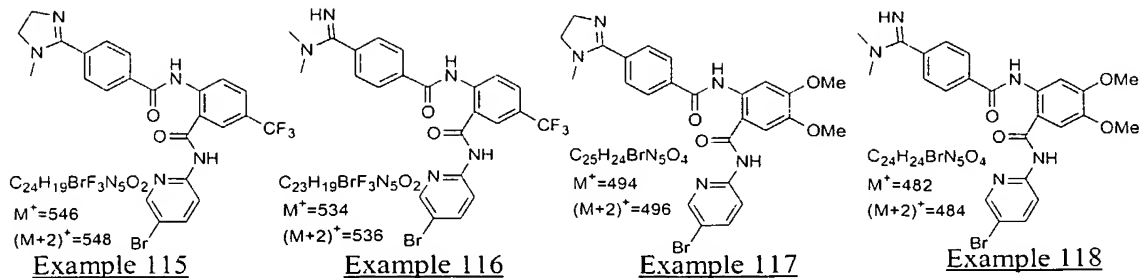
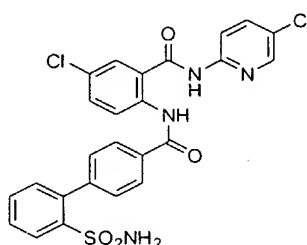
Step 3: To a solution of the compound of (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570mg, 1.49mmol) in dichloromethane (5ml) was added 3-cyanobenzoyl chloride (247mg, 1.49mmol) and pyridine (0.362ml, 4.48mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide as a solid (680mg, 69%). MS found for C₂₃H₁₉BrN₄O₅ M⁺=511, (M+2)⁺=513.

Step 4: To a solution of the compound of N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide (680mg, 1.33mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.586ml, 6.65mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder (240mg, 32%). MS found for C₂₆H₂₆BrN₅O₅ M⁺=568, (M+2)⁺=570.

Examples 115-118

The following compounds were prepared according to the procedure previously described

188

Example 119

5

Step 1: To a solution of 4-{2-{{(tert-butyl)amino}sulfonyl}phenyl}benzoic acid
 (167mg, 0.5mmol) in dichloromethane (5ml) was added oxalyl chloride (0.09ml,
 1mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2
 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane
 (5ml). The compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-
 10 pyridyl))carboxamide (0.17g, 0.6mmol) and pyridine (0.122ml, 1.5mmol) were added
 to the solution. The mixture was stirred at r.t. overnight. The solvent was evaporated
 to give (2-{[4-(2-{{(tert-butyl)amino}sulfonyl}phenyl)phenyl]-carbonylamino}-5-
 chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide. MS found for C29H26Cl2N4O4S
 15 $M^+ = 597$, $(M+2)^+ = 599$.

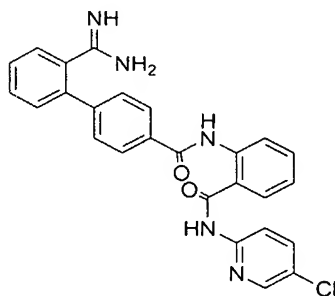
Step 2: The mixture of the compound of (2-{[4-(2-{{(tert-
 butyl)amino}sulfonyl}phenyl)phenyl] carbonylamino}-5-chlorophenyl)-N-(5-
 chloro(2-pyridyl))carboxamide example 12 (0.5mmol) in trifluoroacetic acid (5ml) was
 20 stirred at r.t. for 5hrs. After the evaporation of solvent, the crude residue was purified
 by RP-HPLC to give N-(5-chloro(2-pyridyl))(5-chloro-2-{[4-(2-sulfamoylphenyl)-
 phenyl]carbonylamino}phenyl)-carboxamide as a white powder (68mg, 25%). MS

found for C₂₅H₁₈Cl₂N₄O₄S

M⁺=541, (M+2)⁺=543.

Example 120

5 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]-benzenecarboxamidine



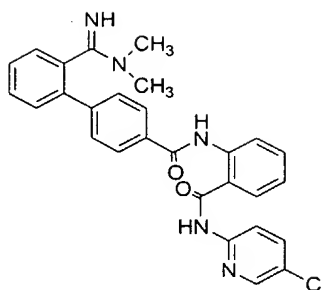
A stream of H₂S (g) was bubbled through a 0 °C solution of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} [4-(2-cyanophenyl)phenyl]carboxamide (100 mg, 0.22 mmol, 1.0 equiv.) in 9 mL pyridine and 1 mL NEt₃ until saturation. The mixture was stirred at rt for 1 day and evaporated. The resulting residue was treated with MeI (94 mg, 0.663 mmol, 3.0 equiv.) in 10 mL acetone at reflux temperature for 1 hr and concentrated to dryness. The resulting residue was treated with a mixture of NH₄OAc (340 mg, 4.42 mmol, 20 equiv.) in 0.5 mL acetic acid and 2 mL methanol at 50 °C for 2 days. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.1% TFA in H₂O/CH₃CN to give 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzenecarboxamidine (15 mg, 15%). MS found for C₂₆H₂₀ClN₅O₂ (M+H)⁺: 470.

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Example 121

(4-{2-[(dimethylamino)iminomethyl]phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide

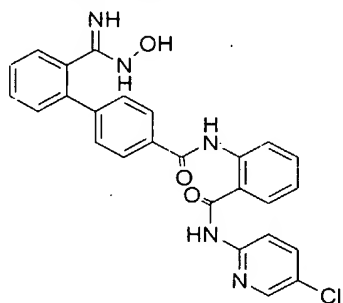
190



This compound was prepared according to the procedure previously described. MS found for $C_{28}H_{24}ClN_5O_2$ ($M+H$)⁺: 498.

5 Example 122

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide



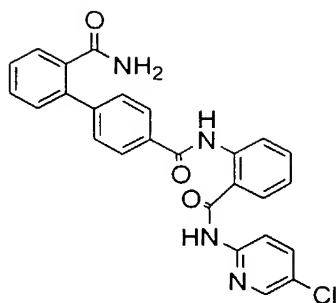
A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-(2-cyanophenyl)phenyl} carboxamide (14 mg, 0.03 mmol, 1.0 equiv.), hydroxyamine hydrochloride (6.25 mg, 0.09 mmol, 3.0 equiv.) and triethyl amine (0.03 mL, 0.3 mmol, 10.0 equiv.) in ethanol (3 mL) was stirred at rt for 6 days, concentrated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl) phenyl] phenyl}carboxamide (4 mg, 27.5%).

MS found for $C_{26}H_{20}ClN_5O_3$ ($M+H$)⁺: 486.

Example 123

2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzamide

191

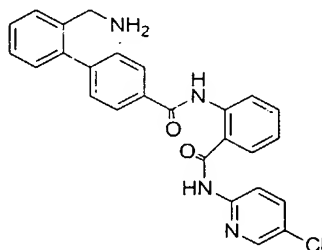


This compound was obtained as one of the side product in Example 122.

MS found for $C_{26}H_{19}ClN_4O_3$ ($M+H$)⁺: 471

5 Example 124

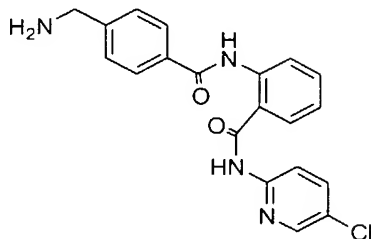
{4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-phenyl}carboxamide



- A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl] carboxamide (200 mg, 0.442 mmol, 1.0 equiv.), cobalt chloride (86 mg, 0.664 mmol, 1.5 equiv.) and sodium borohydride (50 mg, 1.33 mmol, 3.0 equiv.) in DMF (15 mL) was stirred at 0 °C to rt for 3 days. The reaction was quenched with ice cubes, diluted with DCM (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H₂O/CH₃CN gave {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (87 mg, 43%). MS found for $C_{26}H_{21}ClN_4O_2$ ($M+H$)⁺: 457.

20 Example 125

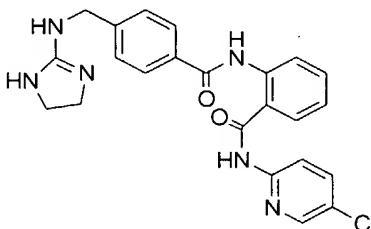
[4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1 g, 2.6 mmol, 1.0 equiv.), cobalt chloride (0.5 g, 3.85 mmol, 1.5 equiv.) and sodium borohydride (0.295 g, 7.8 mmol, 3.0 equiv.) in DMF (20 mL) was stirred at 0 °C to rt for 2.5 hr. The reaction was quenched with ice cubes, diluted with ethyl acetate (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H₂O/CH₃CN gave [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (320 mg, 30%). MS found for C₂₀H₁₇ClN₄O₂ (M+H)⁺: 381.

Example 126

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]-phenyl}carboxamide

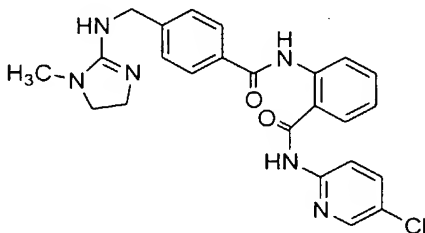


A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (80 mg, 0.21 mmol), 2-methylthio-2-imidazoline hydriodide (77 mg, 0.315 mmol, 1.5 equiv.) and triethyl amine (0.5 mL) in 1 mL DMF was stirred at room temperature overnight, concentrated to dryness and HPLC (C18 reversed phase) eluting with 0.1% TFA in H₂O/CH₃CN gave N-{2-[N-(5-

chloro(2-pyridyl))carbamoyl]phenyl} {4-[(2-imidazolin-2-ylamino)methyl]phenyl}carboxamide (13.5 mg, 15%). MS found for $C_{23}H_{21}ClN_6O_2$ (M+H)⁺: 449

5 Example 127

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide



Step 1: To the boiling solution of 2-methylthio-2-imidazoline hydriodide (1 g, 8.4 mmol) in methanol (10 mL) was added MeI (0.78 mL, 12.6 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred at reflux temperature for 1 hr, concentrated and crystallized with ether to give 1-methyl-2-methylthio-2-imidazoline (1.1 g, 100%). MS found for $C_5H_{10}N_2S$ (M+H)⁺: 131.

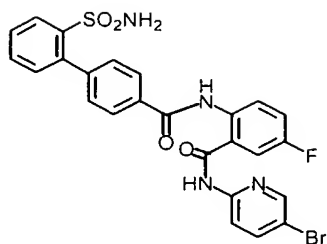
15

Step 2: A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (74 mg, 0.195 mmol), 1-methyl-2-methylthio-2-imidazoline (25 mg, 0.195 mmol), NEt₃ (2 mL) and pyridine (5 mL) was stirred at 80 °C overnight, concentrated and HPLC (C18 reversed phase)eluting with 0.1% TFA in H₂O/CH₃CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide (52 mg, 65%). MS found for $C_{24}H_{23}ClN_6O_2$ (M+H)⁺: 463.

25 Example 128

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide.

194



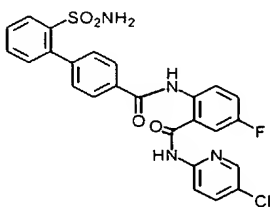
Step 1: A solution of 5-fluoro-2-nitrobenzoic acid (10.0 g, 54 mmol, 1.0 equiv), 2-amino-5-bromopyridine (12.2 g, 1.3 equiv), in 80 mL of pyridine was treated with phosphorous oxychloride (25.3 g, 3.0 equiv) for 30 min. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated. The volatile was evaporated, and the product was triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (12.5 g, 68%). MS found for C₁₂H₇BrFN₃O₃ (M+H)⁺: 340, 342.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (2.0 g, 5.88 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with SnCl₂·2H₂O (5.90 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous NaHCO₃ and 1N NaOH. The organic layer was dried over MgSO₄, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (1.79 g, 98%). MS found for C₁₂H₉BrFN₃O (M+H)⁺: 310, 312.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.310 g, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (0.430 g, 1.3 equiv), pyridine (2 mL) in 10 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was triturated with diethyl ether, and then with chloroform to give N-(5-

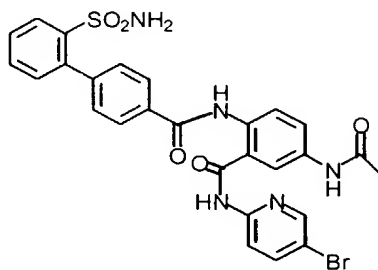
bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%). MS found for $C_{25}H_{18}BrFN_4O_4S$ (M+H)⁺: 569, 571.

5 Example 129



This compound was prepared according to the procedure described in example 2 with the exception of using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in
10 H₂O/CH₃CN. MS found for $C_{25}H_{18}ClFN_4O_4S$ (M+H)⁺: 525, 527.

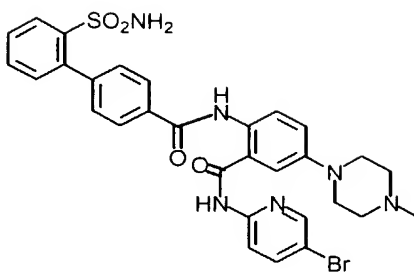
Example 130



This compound was prepared according to the procedure described in example 2 with
15 the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN MS found for $C_{27}H_{22}BrN_5O_5S$ (M+H)⁺: 608, 610.

Example 131

196

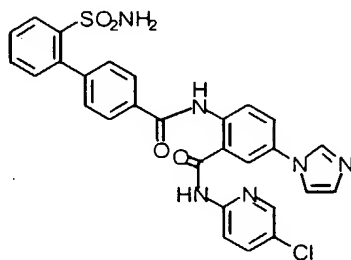


This compound is prepared according to the procedure described in example 2 with the exception of the following step 1b performed on the nitro-intermediate from step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5%

5 TFA in H₂O/CH₃CN MS found for C₃₀H₂₉BrN₆O₄S (M+H)⁺: 649, 651.

Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs₂CO₃ (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90°C overnight. Ethyl acetate
 10 was added and washed with H₂O. The organic layer was dried over Na₂SO₄, filtered, evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54g, 65%). MS found for C₁₇H₁₈BrN₅O₃ (M+H)⁺: 419, 421.

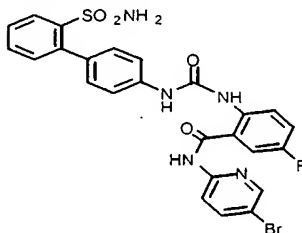
15 Example 132



This compound was prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN MS found for C₂₈H₂₁ClN₆O₄S (M+H)⁺: 573, 575.

Example 133

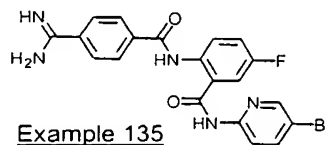
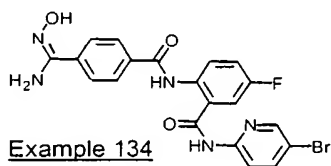
N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.



- 5 Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpholine (0.5 mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was
- 10 redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-
- 15 pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%). MS found for C₂₅H₁₉BrFN₅O₄S (M+H)⁺: 584, 586.

Examples 134-135

- 20 **N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.**



Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine

(3 mL) in 15 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.14 g, 65%). MS found for C₂₀H₁₂BrFN₄O₂ (M+H)⁺: 439, 441.

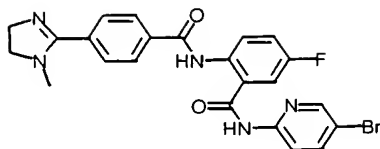
Step 2: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.12 g, 2.56 mmol, 1.0 equiv), hydroxylamine-HCl (0.213 g, 1.2 equiv), and triethylamine (1 mL) in 15 mL of ethyl alcohol was stirred at 50°C overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 194) (0.84 g, 70%). One third of this material was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to yield 0.20 grams (71%). MS found for C₂₀H₁₅BrFN₅O₃ (M+H)⁺: 472, 474.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (0.56 g, 1.19 mmol, 1.0 equiv) and zinc dust (0.39 g, 5.0 equiv), in 10 mL of acetic acid was stirred at rt for 45 min. The volatile was filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenyl-carboxamide (compound Example 195) (0.24 g, 44%). MS found for C₂₀H₁₅BrFN₅O₂ (M+H)⁺: 456, 458.

Example 136

N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide.

199



Step 1: A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.0 g, 2.3 mmol) in 30 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. One-fifth of the resulting residue was treated with (2-aminoethyl)methylamine (0.10 g) in 10 ml methanol at rt overnight. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide (0.082 g, 37%). MS found for C₂₃H₁₉BrFN₅O₂ (M+H)⁺: 496, 498.

Examples 137-198

The following compounds were prepared generally according to the procedure described in Example 196.

